

Treatment of Orthopaedic Infections



Carsten Törholm

University Department of Orthopaedics in Lund
1984



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TREATMENT OF ORTHOPAEDIC INFECTIONS

av

CARSTEN TÖRHOLM

leg läk

Sydsåanska nationen

AKADEMISK AVHANDLING

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Abstract The purpose of the investigation was to evaluate the effect of different methods of treatment in severe chronic bone and joint infections. Forty-eight cases of chronic osteomyelitis or bacterial arthritis operated on with eradication of infectious lesions were randomly treated either by insertion of suction-irrigation drainage or by implantation of gentamicin beads. The average follow-up time was two years. There was no difference in the recurrence rate between the two groups. The gentamicin treated patients were, however, more easily cared for as the suction-irrigation drainage required constant attention. Local temporary treatment with gentamicin beads could be used in cases of deep gramnegative muscle and skeletal infections where it would otherwise be necessary to give toxic antibiotics. Eighteen cases (17 patients) of chronic diaphyseal osteomyelitis with repeated exacerbations have been operated on by intramedullary reaming in addition to the conventional local surgery and antibiotic therapy. Nine patients with severe pain at rest were promptly relieved by the operation. The observation time was 6.3 years. Four patients had relapses of the infection. The remaining patients have "healed". Twenty patients with bacterial arthritis with either delay in diagnosis or no response to treatment were treated with synovectomy. Even when performed after five days and up to four weeks later the synovectomy could prevent joint destruction in the knee but not in the hip. The average follow-up time was 5 years. Twenty-four patients with active, or quiescent septic coxitis have been treated with THR using gentamicin-containing bone cement and longstanding antibiotic treatment. At the follow-up averaging 5.3 years postoperatively there were no recurrences of the infection and the functional results were good. The excretion pharmacokinetics in urine of gentamicin (GM) following total hip joint arthroplasty with GM-impregnated bone cement were studied in ten patients. The patients received 0.5-1.1 g of GM. The levels of excretion and the amount of drug potentially available for antimicrobial action at the cement-tissue interface at various times were determined. Moreover, the biphasic release of GM from the cement was confirmed, as well as the irregular absorption of GM released from the cement. The terminal half-life of the excretion profile was considerably longer than could be explained by the uptake of GM in and the slow release from renal parenchyma, proving that the cement continues to release GM in vivo for long periods.	
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Treatment of Orthopaedic Infections

Carsten Törholm

University Department of Orthopaedics in Lund
1984



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Sjöbo 1984

To my family

Inledning

till

Läran om Friska Sår,

Akademisk Afhandling,

med

Kongl. Maj:ts Allernådigste tillstånd

och

Akademiska Konsistoriets i Lund samtycke

till offentlig granskning framställd

af

HERRMAN IMMANUEL CARLSON

Medicinæ Doctor & Chirurgiæ Magister

och

MAGNUS FÜRST

Med. Philos. Candidat.

på Carolinska Akademien den 28 Nov. 1846.

Lund,

tryckt uti Berlingska Boktryckeriet,
1846.

Starkt contunderade eller med bensplitt-ring förenade sår hafva företrädesvis benägenhet att af Warfeber angripas, och, i allmänhet, complicerade sår mer än enkla. Såsom uppväckande orsaker kunna räknas dels smitta och bristande renlighet hos de skötande eller den sjuke, dels någon gång ett ovarsamt utsättande af det öppna såret för luftens åverkan.

Prognosen är i denna sjukdom, måhända utan undantag, att anse såsom hopplös. Det är också kanske icke fullkomligt rätt att kalla den en själfständig sjukdom; åtminstone är det för Läkaren alltför nedslående att tänka sig en sjukdom med acut förlopp finnas, om hvilken vi ej veta att den någonsin blifvit botad. Lika nära sanningen kunde man också vara vid att kalla Warfebern en döds-kamp snarare än en sjukdom, ty sedan blodet redan blifvit till en betydelig del uppblandadt med elakartadt war och sjelft börjat undergå förändring till sin egen både fysiska och kemiska sammansättning, då är rimligtvis icke mer att tänka på hälsans återställande eller ens på lifvets bibehållande. Kan man ej förebygga detta tillstånds inträdande, att upphäfva det eller göra det oskadeligt, dertill räcker den mensklige förmågan, åtminstone efter vetenskapens och konstens närvarande ståndpunkt, icke långt.

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The thesis is based on the following publications, which will be referred to by their Roman numerals:

- I. Hedström S-Å, Lidgren L, Törholm C, Önnarfält R. Antibiotic containing bone cement beads in the treatment of deep muscle and skeletal infections. Acta Orthop Scand 1980;51:863-9.
- II. Lidgren L, Törholm C. Intramedullary reaming in chronic diaphyseal osteomyelitis. Clin Orthop 1980;151:215-21.
- III. Törholm C, Hedström S-Å, Sundén G, Lidgren L. Synovectomy in bacterial arthritis. Acta Orthop Scand 1983;54:748-53.
- IV. Törholm C, Lindberg L, Josefsson G, Carlsson AS. Total hip replacement with gentamicin bone-cement after septic arthritis. Submitted for publication in Acta Orthop Scand 1983.
- V. Törholm C, Lidgren L, Lindberg L, Kahlmeter G. Total hip joint arthroplasty with gentamicin-impregnated cement - a clinical study of gentamicin excretion kinetics. Clin Orthop 1983;181:99-106.

INTRODUCTION

Orthopaedic infections, i.e. infection of bone and joints, often extending to the surrounding soft tissues, have long been recognized as being in a class of their own. The clinical picture of chronic bone infection was described already in the Smith papyrus from 5 000 to 3 000 B.C. (1), and more extensively by Arderne in the 13th century (2).

Robinson (3) concluded in 1927 that so much had been written on osteomyelitis that he hesitated to make any further contribution. A large documentation can be found especially in countries that had been at war during the last century. Increased urbanization, traffic, industrialization and more extensive surgical procedures mean that the total number of chronic osteomyelitis will not decrease despite a reduced frequency of postoperative and posttraumatic infections.

The general principles for treatment of orthopaedic infections have recently been extensively reported from the center of orthopaedic infections in Lund (2,4,5,6). This study concentrates on cases not responding to the generally employed antibiotic and surgical principles.

Osteomyelitis:

Recently the annual incidence in Hungary of new cases of chronic osteomyelitis of the posttraumatic, postoperative or hematogenous kind was estimated at 15-30/100 000 inhabitants (7) during the last five year period, a figure that well matches the statistics from Sweden (8,9).

The annual incidence of acute hematogenous osteomyelitis in Sweden has been calculated to be 3-4/100 000 (8) half of which is juvenile (10).

The number of cases of acute hematogenous osteomyelitis developing into chronic osteomyelitis have been reduced by early antibiotic treatment and surgical decompression from 10-20 per cent to less than 2 per cent (11,12).

Antiseptic and aseptic principles introduced during the 19th century reduced the previous high mortality rate in postoperative and post-traumatic infection. In the late 19th century before the studies of Pasteur and their application by Lister in 1867 (13), one third of all patients with open tibial fractures died (14). In fracture surgery today infections are rarely fatal and the evaluation of the result of treatment is based on bone alignment and function. Infection and/or non-union are regarded as definite failures. The surgical treatment of chronic osteomyelitis is often a question of healing a fracture and eventually the infection.

The definitions of acute and chronic osteomyelitis as well as the classification of the various forms of the latter have been a source of much controversy. The Anglo-Saxon countries have accepted a change in classification from acute to a chronic phase when local ischemic changes have occurred, i.e. after 2-3 days (15,16). A localized osteomyelitis without a fulminant clinical picture is called a Brodie abscess, histologically characterized by a center of granulation tissue with round cells (17). A similar radiographic picture can be seen with a dominance of plasma cells and is then called plasmacellular osteomyelitis (17,18). A sclerosing form with increased bony density, periosteal reaction, reduced circulation and sometimes a totally obliterated medullary cavity is the Garré osteomyelitis (19).

The various types of hematogenous progressive osteomyelitis could be individual reactions to differences in the individual immunity to different bacterial antigens (20).

It is obvious that the treatment of the various types of hematogenous chronic osteomyelitis has to be individualized and based on

previous clinical, radiographic and therapeutic experience.

The frequency of relapses in chronic osteomyelitis treated during the last decade with at least five years of follow-up is on average 20 per cent (4-35 per cent) (21). Intervals of as much as 49 years before relapse have been reported (22).

Patients with osteomyelitis have often been operated on repeatedly. The infection can be located either in a difficult anatomic region or occupy such a large area that a radical surgical procedure is almost impossible without subsequent disability. In cases with haematogenous chronic osteomyelitis, radical surgery could mean a total resection of a long tubular bone. It is of great importance that methods be developed which limit bone resection as, for instance, in fracture surgery where only devitalized tissue or bone should be removed to avoid jeopardizing fracture healing.

Bacterial arthritis:

The annual incidence of bacterial arthritis has been estimated to be 3/100 000 of which one third occurs in juvenils (8,23).

In the pre-antibiotic era one third of the patients with bacterial arthritis died (24). This mortality rate was reduced to 0-12 per cent with the introduction of penicillin, and now occurs mainly in patients with concomitant diseases (25,26,27).

During the last decade several authors have reported joint destruction with impaired function in one third of all affected joints (27,28,29). Bacterial arthritis is also regarded as a relative contraindication for inserting of joint prostheses (30).

Deep infection in total hip replacement:

Deep infection is a serious complication after total hip joint replacement. In the 1960s and the beginning of the 1970s the post-operative infection rate in large materials was 8-15 per cent (31, 32). Strict hygienic routines, clean-air operating enclosures and

the use of preoperative systemic antibiotic prophylaxis have reduced the infection rate to 1 per cent or less (32,33,34,35). In 1970 Buchholz and Engelbrecht (36) introduced the concept of adding antibiotics to bone cement. In a clinical randomized study gentamicin-impregnated bone cement was shown to be at least as effective as systemic antibiotics (37). The long-term effect of antibiotic impregnated cement on hematogenic infections has not been proven (38,39,40).

Total hip revision in infected cases with the use of antibiotic loaded bone cement and systemic antibiotics has shown good results in more than three fourths of the cases with an average follow-up of three years (31).

On the basis of his experience of revision of infected total hip arthroplasties, Klemm in 1976 (41) introduced an antibiotic bone cement in beads for the treatment of osteomyelitis. The release of GM (gentamicin) from bone cement in vitro has been thoroughly investigated but in vivo pharmacokinetic calculations are few.

The aim of the present investigation was:

- I. To compare local treatment with gentamicin bone cement beads with conventional treatment using suction-irrigation drainage in a series of patients with chronic bone and joint infections.
- II. To see if the addition of intramedullary reaming to the conventional local eradication could improve the result in long-standing chronic osteomyelitis.
- III. To see if in patients with bacterial arthritis, with either delay in diagnosis or no response to earlier antibiotic treatment, synovectomy could reduce the frequency and/or the degree of joint destruction.
- IV. To see if total hip replacement with gentamicin-containing bone cement could be safely performed after a recent or past history of septic arthritis.
- V. To investigate the in vivo pharmacokinetics of gentamicin excretion following total hip replacement with gentamicin cement and to determine the influence of gentamicin accumulation in renal parenchyma on the excretion kinetics.

PATIENTS, METHODS AND RESULTS

Antibiotic containing bone cement in the treatment of deep muscle and skeletal infection (I)

This study comprised 47 patients with 48 instances of chronic osteomyelitis or bacterial arthritis. The mean age was 49 years. The indications for operation were an active secreting fistula, severe pain at rest or repeated exacerbations. The infection was hematogenous in five cases and post-traumatic after open fractures in six.

There were 37 postoperative infections of which 33 had implanted foreign material. The average duration of the disease was 10 years. The patients were randomly assigned to treatment with either gentamicin beads or suction-irrigation drainage.

The bacteriologic cultures were classified as positive, only if repeated samples taken from fistulas on several occasions showed growth of the same bacteria, or if more than three out of five cultures taken during the operation from various sites in the operation area showed identical bacteria. The most common bacterium found was *Staphylococcus aureus*; furthermore seven out of 46 positive cultures showed growth of *Pseudomonas pyocyanea*.

Twenty-three patients were treated with gentamicin beads and 25 by the conventional technique. A complete eradication of the infectious lesion was aimed at in all instances. The foreign material was usually extracted, but in cases of unhealed fractures the fixation was retained until the fracture had healed.

To evaluate the extent of devitalized tissue, intravital staining with Disulphine Blue (ICI, Great Britain) was used in nine cases. The beads were inserted into bone as well as soft tissue. The remaining cavities were filled at operation with beads, the number varying from eight (36 mg gentamicin base) to 540 (2 430 mg gentamicin base). The beads were left in position, usually with one bead outside the skin

to facilitate removal which was done two weeks later. The average treatment duration with closed suction-irrigation drainage was four days. Ten to 15 liters of Ringer's solution kept at body temperature was circulated continuously throughout the operation area. The suction-irrigation period ended with two days of suction drainage only. All patients received systemic antibiotics after the culture specimens were taken. This antibiotic treatment was continued for an average of seven months postoperatively.

All patients were re-examined at an average of 24 months postoperatively. Two recurrences were noted in the group treated with gentamicin beads. Four recurrences were noted in the group treated with suction-irrigation drainage. The average length of time spent in hospital for the group treated with gentamicin beads was 27 days of which three were spent in bed. The figures for the suction-irrigation group were 22 and 5 days, respectively.

Twenty-two of the patients had non-united fractures and chronic osteomyelitis. These fractures had all healed at re-examination. The gentamicin concentrations in the wound secretion, blood and urine for nine patients examined are shown in Figure 1.



Fig 1. Gentamicin concentrations in serum, wound secretion and urine after implantation of gentamicine - polymethylmethacrylate beads (mean 140 beads, range 18-540) in nine patients with chronic osteomyelitis. Gentamicin concentrations were determined by G. Kahlmeter, Department of Medical Microbiology, Lund, Sweden, using a previously described agar well diffusion technique (Kahlmeter et al. 1978).

Intramedullary reaming in chronic osteomyelitis (II)

The material comprised 18 cases of chronic diaphyseal osteomyelitis in 17 patients with repeated exacerbations, fistulation or severe pain or both. The mean age was 45 years. The average duration of the disease was 19 years. The local infectious lesion was first extirpated, after which intramedullary reaming with a Küntscher drill was carried out from proximally and distally to the osteomyelitic lesion through separate drill holes in the metaphyses. Reaming of the chronic osteomyelitis with an open marrow cavity was not difficult and the purpose in these cases was primarily to clean out the medullary cavity. However, in sclerotic obliterated marrow cavities the operation was laborious. As a rule, a sharp guide had to be forced through the sclerotic bone before a 9-mm drill could be used. This was then changed to a blunt guide for reaming up to 11-13 mm for the tibia and 15-18 mm for the femur.

In addition to the reaming, conventional treatment was performed with suction-irrigation drainage or gentamicin polymethylmethacrylate beads.

After the culture specimens were taken all patients received antibiotics intravenously during the operation. Postoperative antibiotics were administered perorally for an average of ten months according to the sensitivity pattern. Cloxacillin was given in 15 cases and cephalotin in three.

The postoperative observation period was 28 (16-53) months. Two patients had recurrences. One fistula did not heal but the patient was relieved of his pain. The other patient had a soft-tissue abscess with growth of the same bacteria four weeks after operation. The abscess was incised and the patient was symptom-free 29 months after the operation. The remaining 16 patients did not show any signs of recurrence. Nine of the patients had marked pain at rest or at weight-bearing before the operation. Eight of these became free from pain. One had only slight pain at weight-bearing, compared with severe pain, even at rest, before the operation.

Eight of 15 patients with recurring fistulation had severe psychological problems before the operation, believing that they were unhygienic and guilty of contaminating the environment. All of these patients were markedly relieved after the operation.

There were no complications except for an oblique fracture of the femur through the proximal drill hole in a 14-year-old boy who sustained a minor trauma four weeks postoperatively. The fracture was treated by traction and cast-brace and healed uneventfully.

Since then the patients have again been investigated on average 6.3 years (range 5.3-8.4 years), after the operation. Of the 16 patients who were considered healed on average 28 months after the operation, 14 had had no recurrence.

Two patients relapsed after 3 and 4 years, respectively. They are being treated with Flucloxacillin orally 1 g three times daily and Probenecid 2 g two times daily and have now no fistulation and/or pain.

Synovectomy in bacterial arthritis (III)

During the period 1973-1980, 20 patients (mean age 42 years) with bacterial arthritis were synovectomized. They were categorized into three groups on the basis of the delay in diagnosis and thus the delay in treatment (see Table 1 below).

The criteria for infection in these patients was at least one of the following:

- 1/ positive culture taken by sterile aspiration
- 2/ positive culture biopsy from the synovium
- 3/ radiographic changes showing osteomyelitis
- 4/ fistulation from the joint

The antibiotic treatment during the period, either Cefuroxim or a combination of Cloxacillin and Ampicillin, was given parenterally for 1-2 weeks followed by peroral isoxazolympenicillin or a cephalosporin for an average of four months. Antibiotic treatment was generally started after joint fluid analysis without waiting for the culture result.

In all bacterial coxitis or postoperative infections an arthrotomy was performed immediately after diagnosis. Hematogenous bacterial arthritis in other joints was initially treated by repeated aspiration and irrigation of the joint and if the symptoms had not decreased within one to two days or if pus was found, an arthrotomy as above was performed.

For coxitis we used a dorsal approach and the femoral head was not dislocated. Most of the pannus could be removed by rotating the femoral head. The joint was drained and flushed with physiological saline, several times during the operation, a thick drainage was left in the joint cavity and the wound closed with few sutures.

For the knee joint a para-patellar medial incision with luxation of the patella was used. In cases of pannus growing over the cartilage this was removed. All granulation tissue around the collateral and crucial ligaments was removed. In cases of underlying bone destruction the osteomyelitic process was carefully removed. The operation was performed when possible in a bloodless field. Continuous suction-irrigation drainage with 10-15 l Ringer acetate solution was instituted for 3-8 days followed by two days of suction drainage.

The affected hip or knee joint was immobilized the first postoperative week. Active motion without weight-bearing was followed by gradual weight-bearing after six weeks. If the flexion of the knee joint after two weeks of active training was less than 90 degrees a mobilization in general anaesthesia was performed. The patients were followed clinically and radiographically for an average period of five years.

The results (Table 1) were graded as follows:

- Good: Patients with no pain, normal motion, normal radiogram and normal daily activity.
- Fair: Radiogram showing narrowing grade 2 (according to Ahlbäck 1968), slight pain at weight-bearing, and slight limitation of mobility.
- Poor: All remaining patients.

Table 1

Group	<u>Delay in treatment</u>		<u>Follow-up</u>			Total
	Days	Mean duration	Hip		Knee	
I	0-5	3	2 good	1	good	3
II	6-28	21	1 poor	12	10 good 2 fair	13
III	> 28	180	3 poor	1	good	4
Total			6	14		20

There were no recurrences of infection

Two patients in group II with an average delay of 15 days had fractures of the patella and the lateral tibial condyle, respectively. These are the two patients rated "fair". In group III one patient had symptoms for six months and synovial tuberculosis. Eight years later he had a normal knee joint, clinically and radiographically. All three patients in group III with coxitis had advanced bone destruction, two of them treated with resection of the femoral head and later on a successful total hip arthroplasty. The third patient had a severely destroyed hip with a motion of 10-45 degrees in extension-flexion but no pain.

Total hip replacement with gentamicin bone-cement after septic arthritis (IV)

The material consisted of 24 consecutive patients with septic coxitis or an infected hemiarthroplasty operated on between October 1975 and July 1980 with total hip replacement and gentamicin-containing bone cement.

The operations were performed at the Departments of Orthopaedics in Lund, Malmö and Gävle, Sweden. There were 14 women and 10 men. The age at the time of the total hip replacement averaged 63 years.

In 20 cases the infections were subsequent to the following operations: nailing of a femoral neck fracture (16) uncemented hemiarthroplasty (3), and open fixation of an acetabular fracture (1). In the remaining four the infection was hematogenous. There were radiographical signs of advanced septic arthritis in all cases, i.e. progressive destruction of the hip joint and osteomyelitis in adjacent bone tissues.

In 16 cases the total hip replacement was performed without any other prior surgical treatment than drainage of an abscess or extraction of the osteosynthetic material. After debridement of the infected tissue the total hip prosthesis was implanted with the use of gentamicin-containing bone cement. In three cases all infected tissue was first removed, the wound filled with gentamicin PMMA beads and then primary sutured. After four weeks the beads were removed and a total hip prosthesis implanted using gentamicin-containing bone cement.

In the remaining five patients referred from other hospitals, the primary treatment was different. In three cases suction-irrigation drainage was applied followed by total hip replacement after 3, 13 and 32 months, respectively, and the last two hips were uncemented hemiarthroplasties replaced by a total hip 7 respectively 39 months after removal of the prosthesis.

Tissue biopsies for aerobic and anaerobic bacteriological cultures were obtained in all cases. Antibiotic therapy was instituted and continued for an average period of five months.

The evaluation of the infection at the time of the total hip replacement was based on the ESR, the presence of a draining fistula and positive cultures obtained at the time of the total hip arthroplasty.

The patients were assigned to one of the following groups:

- I Active infection: positive culture.
- II Probably active infection: negative cultures but elevated ESR which became normal after the total hip replacement, and/or a draining sinus.
- III Healed or quiescent infection: negative culture and preoperatively normal ESR.

There were 4 active infections, 8 probably active and 12 healed or quiescent infections.

The patients were followed for an average of 62 months after the hip replacement.

The function was evaluated according to Merle d'Aubigné and Postel (42) as modified by Charnley (43), see Table 2.

All patients exhibited primary wound healing. There were no clinical, laboratory or radiographic signs of infection. Three patients who died from causes other than their hip condition 20, 41 and 85 months postoperatively had no signs of recurrence of the infection.

Fifteen patients were completely free from pain. The remaining nine had slight or intermittent pain decreasing with activity. Walking ability was normal or nearly normal for 11 of the 13 category A patients.

In 11 cases there was no leg length discrepancy, in 11 less than 2 cm of shortening and in two cases shortening of between 2 and 5 cm.

Four of the category A patients demonstrated a positive Trendelenburg sign whereas it was negative in the rest of this group.

Table 2. The function of the hip at re-examination

		No of pat	Hip score						Average
			1	2	3	4	5	6	
Pain	Cat. A-C	24					9	15	5.6
Walking ability	{ Cat. A	13				2	5	6	5.3
		Cat. B	3			1	2		3.7
		Cat. C	8	1	1	2	4		3.1
Range of motion	Cat. A-C	24		1	1	7	11	4	4.7

One patient developed a small wound abscess with *Staphylococcus aureus* 26 months after the total hip replacement. The wound healed after two weeks of Cloxacillin treatment which was then continued for five months. The patient did not have any pain, ESR increase or radiographic signs of deep infection. The follow-up time is now 19 months.

Total hip joint arthroplasty with gentamicin impregnated cement - a clinical study of gentamicin excretion kinetics (V)

Since the excretion profile of gentamicin (GM) following the introduction of GM bone cement and beads into the body is heavily influenced by the general pharmacokinetics of gentamicin, these characteristics are outlined.

One, two and three-compartment models have been used to describe the pharmacokinetics of gentamicin (50). Like other aminoglycosides, gentamicin is given intravenously or intramuscularly. Following an intramuscular injection of clinically used doses i.e. 1.0-1.5 mg/kg peak-concentrations in serum of 2-8 mg/l are attained after 30-90 min (50). The drug is water soluble and is rapidly distributed in the interstitial fluid of most tissues. The apparent volume of distribution is approximately 25 per cent of the body weight in adults.

Penetration of biological membranes is otherwise poor. Concentrations in cerebrospinal fluid, joint and peritoneal fluid, sputum, abscesses etc. are low and only marginally increased in the presence of inflammatory processes. Protein binding is below 10 per cent.

Elimination of gentamicin occurs mainly by glomerular filtration; metabolism is not considered to contribute significantly to the elimination of the drug (50).

Approximately 10-15 per cent of a single intravenous dose is reabsorbed by the proximal tubular cells and then bound intracellularly. The process is thought to be capacity-limited. The drug is firmly bound and only slowly released. The concentration curves in serum and urine following parenteral administration are biphasic; in patients with a normal renal function the initial phase exhibits a half-life, dependent on the glomerular filtration rate (GFR), of 1.5-2.0 hours. The terminal phase, apparent both in serum and urine, is GFR independent and mainly governed by intracellular binding kinetics.

GM exhibits a half-life of 30-60 hours in healthy volunteers and of 150-200 hours in hospitalized patients (50,51).

Ten patients (mean 63 years) undergoing total hip joint replacement with polymethylmethacrylate (PMMA) bone cement containing 0.89 per cent active gentamicin sulphate were investigated (Fig. 2). They received 7.34 g of Palacos^R and thus 0.65 g of gentamicin (corresponding to 9.6 mg/kg). Four, 12 or 24 hour portions of urine were collected for up to two years postoperatively. Gentamicin concentrations in urine were initially 8-25 mg/l and during the first four days the daily excretion ranged from 0.7-25 mg/day. On the 30th day the drug levels in urine were 0.5-1 mg/day. The excretion time curve (Fig. 2) consisted of an initial rapid phase which terminated 4-6 days postoperatively with a half-life of 0.65 days and a slow phase with a half-life of 16 days.

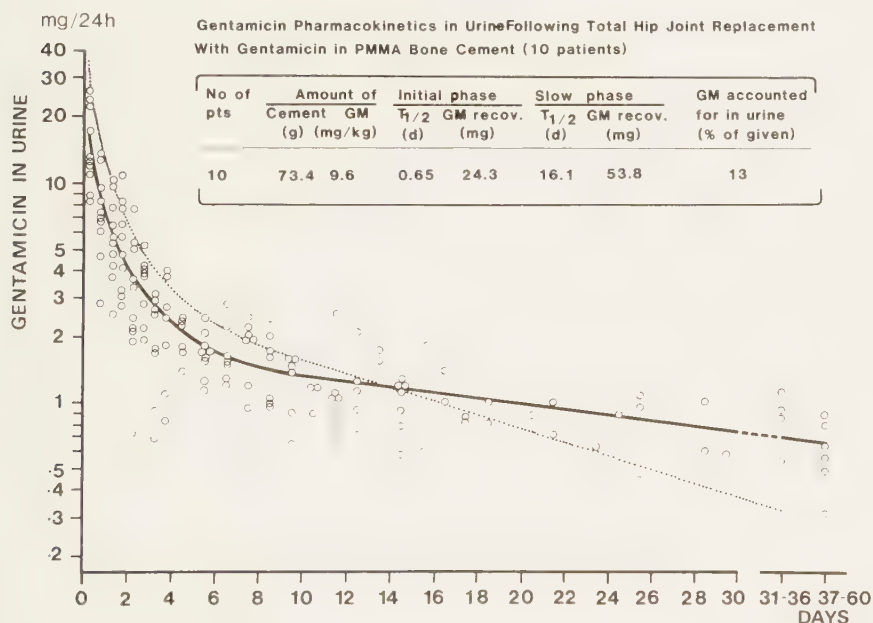


Fig 2. Excretion of GM in urine (mg/day). Individual values and mean curve (unbroken line) in 10 patients following total hip joint arthroplasty with 0.9 % GM base in the PMMA cement (mean dose, 9.6 mg/kg; range 5.6-16.7 mg/kg). Dotted line = mean excretion curve in 16 patients following 5-22 days of parenteral GM therapy for various infections (total dose, 15-60 mg/kg) (see Kahlmeter et al. (50)).

The amount of gentamicin recovered during the initial phase was 24 mg and during the slow phase 54 mg. The latter amount includes the extrapolated area under the curve. The total recovery corresponds to 13 per cent of the given dose. Although some gentamicin was lost in wound secretion during the first few days, a major part of it remained unaccounted for.

Urine collections obtained two years after the operation in one of eight patients still yielded 0.1 mg/24 hours of gentamicin indicating that the true terminal half-life was longer (> 240 days) than the average 16 days calculated from data 5-60 days postoperatively. Using this data roughly 50 per cent of the gentamicin given could be accounted for.

The dotted line curve in Fig. 1 represents the mean gentamicin urinary excretion time curve in 15 patients following a normal course of parenteral gentamicin therapy for various infections. It is considered to represent the slow release of gentamicin from the renal cortex in these patients and exhibits a half-life of roughly 10 days. The fact that the measured half-lives following gentamicin bone cement and parenteral therapy, respectively, do not coincide indicates that the drug continues to be released from the cement, and is made available to the tissues surrounding the prosthesis.

An attempt to calculate the amount of gentamicin available to the tissues surrounding the cement at 30 days after operation shows that the surface area of the cement would be in excess of 150 cm^2 and the tissue volumes of a 0.1, 0.5 and 1.0 mm thick tissue layer would be 1.5, 7.5 and 15.0 cm^3 , respectively. The amounts of gentamicin available per cm^3 and day were found to be 670, 134 and 67 ug, respectively.

GENERAL DISCUSSION

The difficulties in treating chronic osteomyelitis are well-illustrated by the multitude of methods described in the literature. Cauterization with coals (1500-800 B.C.) (44), iodine pellet fillings (45), and antibiotic-whipped blood mixture have been used in osteomyelitic cavities (46). The combination of radical surgery and antibiotic therapy in the management of most cases of post-traumatic osteomyelitis is currently accepted.

During the last 20-30 years there has been a change in the bacteria causing osteomyelitis from gram-positive i.e. *Staphylococcus aureus* to gram-negative bacteria (47). An increasing number of *Pseudomonas aeruginosa* infections are seen in severely traumatized patients. Effective antibiotic treatment of gram-negative bone infections is often difficult. When *pseudomonas* species are involved an aminoglycoside in combination with a carbenicillin-like beta-lactam compound is usually the only effective alternative. Systemic aminoglycoside therapy, especially when prolonged, carries a risk of serious side effects, i.e. oto- and nephrotoxicity especially in the elderly. Since these side-effects are related to the systemic aminoglycoside concentrations the addition of an aminoglycoside to a carrier, such as bone cement, which yields high concentrations at the site of potential or actual infection, but low systemic concentrations, is an attractive concept.

Local antibiotic treatment was introduced by Jensen (48) in 1937 using sulphonamides and since then several carrier substances such as blood (46), plaster (49) and polymethylmethacrylate PMMA (41), have been tried.

Gentamicin pharmacokinetics (V, I)

Several systemic and local antibiotic regimens have been employed in the prevention of infection after total hip arthroplasty (THA).

The GM-containing bone cement (36) introduced in 1970 has been shown to be effective in the prevention of early infection after total hip arthroplasty and in revisions of infected prostheses (31,37).

Based on data collected from zero to 60 days after the insertion of the cement in total hip arthroplasties it was calculated by extrapolation of the recorded terminal phase that 5-18 per cent of the GM could be accounted for. With the addition of 5-10 per cent lost in wound secretions, 75-80 per cent was still unaccounted for. Since there is no reason to assume any loss by inactivation, or excretion by any other major route, it is assumed that the terminal phase has a considerably longer half-life than that recorded. Data obtained after two years from one of the patients support this hypothesis, suggesting a terminal half-life of at least 240 days in this patient.

Three to four weeks after insertion of the GM bone cement, the 24-hour excretion of the drug in urine was 1 mg or less. Thus, at the most 1 mg of GM/day would be available for antibacterial action at the cement-tissue interface. Whether or not this is sufficient to prevent infection from hematogenously disseminated bacteria is not known.

In animal models in which *Staphylococcus aureus* and/or various gram-negative bacteria were either introduced directly into the bone cavity with the cement or intravenously 30 minutes to six weeks after operation, the infection was successfully prevented (38,39,40). When *Staphylococcus aureus* were injected intravenously six weeks after operation Elson and co-workers (39) found no difference between the experimental and control groups, but the incidence of deep infection in the control group was low (39). Blomgren and Lindgren (52) recorded a high incidence of deep infection in both groups. Thus, it seems that in animal models the long-term protective effect of GM bone cement is doubtful.

Treatment of osteomyelitis I, II

During the last decades suction-irrigation drainage has been used for temporary cleaning of infected cavities (15,53). Successful local temporary treatment with gentamicin beads in deep, subacute and chronic infections of bone and soft tissue has been reported by several authors (21,41,54). In the present investigation implantation of gentamicin beads gave the same recurrence rate as suction-irrigation drainage. The main advantage was that these patients were more easily cared for as the suction-irrigation drainage demanded constant attention and often caused difficulties.

The majority of the infections in our study were caused by *Staphylococcus aureus* but in no less than 7 of 48 cases the responsible organism was *Pseudomonas pyocyanea*. Systemic treatment with toxic preparations could be avoided in these patients and concentration determinations in nine of the patients showed no measurable systemic levels of gentamicin.

There is little reason to leave the gentamicin beads in longer than two weeks, considering the rapid release of gentamicin (Fig. 1) and the difficulties in removing the beads later on.

A complete eradication of all infectious material without unnecessary removal of vital bone, the utmost attention to the skin condition, temporary cleaning of the infected cavity followed in a second stage by massive bone transplantation and stable fixation proved to be effective. Twenty-two of the patients had unhealed fractures and chronic osteomyelitis. All these fractures had healed at re-examination.

In chronic diaphyseal osteomyelitis, sclerotic, poorly vascularized bone is often found (55,56). Long-term antibiotic treatment may diminish pain and even cause healing of fistulae (4). Approximately

20 per cent of such cases have frequent exacerbations which cause continuous pain at rest, disturb sleep and give rise to occasional fistulation. Pain at rest in these cases can be interpreted as a sign of increased intraosseous pressure (57). In this study not only conventional local eradication was carried out, but also intramedullary reaming with the purpose of diminishing the intraosseous pressure and revascularization of the bone, thereby improving the endosteal circulation (56).

Intramedullary reaming had a prompt effect in all the nine cases with severe pain. Although we do not know how long this effect will last, this procedure might well be justified in these severely afflicted patients. All the patients had been operated on before with standard techniques, though not by the authors, most of them several times with almost immediate recurrences and no pain relief. The low number of recurrences are encouraging and indicate that the addition of intramedullary reaming to the usual treatment with local extirpation and antibiotics (15) may be an improvement.

Treatment of bacterial arthritis III, IV

During the last decade many investigations have shown that unless bacterial arthritis is treated intensively with antibiotics within 24-48 hours after onset of symptoms, irreversible joint cartilage damage will result (25,58,59). Increased intra-articular pressure and/or enzymatic degradation are mainly responsible for the cartilage destruction (60,61). Therefore early antibiotic treatment and drainage with irrigation in order to reduce pressure and flush the joint is important (62,63). However, in spite of these treatment principles secondary joint changes have been known to develop and sepsis with a fatal outcome known to occur (26,28,29,64,65). Especially the hip joint is very sensitive and many authors have recommended drainage within the first days (26,28,58,59,62,64,66). We found that synovectomy in bacterial arthritis as indicated by Gérard (67), even when performed with a delay of five days to four

weeks could prevent secondary joint destruction in the knee but not in the hip. The results were also better in comparison with other published materials where synovectomy was not performed.

When bone destruction has occurred it is seldom possible to restore the anatomy. However, it is still important to arrest and eradicate the infection for later reconstructive arthroplastic surgery. The destroyed joint will often cause pain and impaired function.

The method described by Girdlestone (68) for the hip implies resection of the head and neck of the femur and all infected tissues. This method is still used (69) as primary permanent treatment for septic coxitis.

With respect to total hip arthroplasty the difficulties in deciding whether the infection has healed or not has entailed a long wait for final reconstructive treatment. Hardinge et al. (70) recommended great restraint and in their report the time from infection to total hip replacement averaged 10 years. In this series the patients were given prophylactic Cloxacillin for two weeks. There was no recurrence of the infection on average 32 months postoperatively. The corresponding interval in a series reported by Wilson et al. (71) averaged 18 months and the patients had been treated by suction-irrigation drainage and systemic antibiotics for seven weeks. However, the infection persisted (recurred) in 4/36 cases at examination on average 12 months after the total hip replacement. In our series the interval between infection and total hip arthroplasty averaged 17 months (range 3-67) and there were no recurrences on average 62 months postoperatively. From the present study it is shown that a 10-year delay is unnecessary if the total hips are implanted together with gentamicin-containing bone cement.

Naturally, in cases with a flourishing infection the cellulitis must first be treated. However, a total hip replacement could then be safely performed - preferably as a modified two-stage procedure

as described by Hovelius and Josefsson (72) leading to a "Girdle-stone period" of 2-4 weeks.

GENERAL SUMMARY

Forty-eight cases of chronic osteomyelitis or bacterial arthritis operated on with eradication of infectious lesions were randomly treated either by suction drainage irrigation or by implantation of gentamicin beads. The average follow-up time was two years. There was no difference in the recurrence rate between the two groups. The gentamicin treated patients were, however, more easily cared for as the suction-irrigation drainage required constant attention.

Eighteen cases (17 patients) with chronic diaphyseal osteomyelitis with repeated exacerbations were operated on by intramedullary reaming in addition to the conventional local surgery and antibiotic therapy. The average duration of the disease was 19 years. Nine patients with severe pain at rest were promptly relieved. The observation time was 6,3 years. In four patients the infection has relapsed. The remaining patients have "healed".

Twenty patients with bacterial arthritis with either delay in diagnosis or no response to treatment are presented. Synovectomy performed five days to four weeks after initial symptoms prevented joint destruction in the knee but not in the hip. The average follow-up time was five years.

Twenty-four patients with active, probable or healed infection after septic coxitis were treated with THR using gentamicin cement and long-standing systemic antibiotic treatment. At the follow-up averaging 57 months there were no recurrences and the functional results were good regarding pain, walking ability and range of motion.

The excretion pharmacokinetics of gentamicin following total hip joint replacement with gentamicin bone cement were studied in 10 patients.

The GM excretion time curve showed an initial rapid phase terminating 4-6 days postoperatively, with a half-life of 0.65 days, and a slow phase with a half-life of 16 days. It was calculated that approximately 13 per cent of the GM administered was accounted for. Data obtained two years postoperatively suggests that the half-life of the terminal phase is much longer (> 240 days) than that calculated from data obtained during two months postoperatively. It was calculated that the surface area of the cement would exceed 150 cm^2 and that the volume of a 1 mm thick interface tissue layer would be approximately 15 cm^3 . Thus, at three weeks, when the daily excretion was approximately 1 mg/24 h, $67 \text{ ug/cm}^3/\text{day}$ of GM would be available for antimicrobial action at a 1 mm thick tissue/cement interface.

CONCLUSIONS

Local temporary treatment with gentamicin beads can be used in cases of deep muscle and skeletal infections where it might otherwise be necessary to give systemic potentially toxic antibiotics.

The gentamicin beads are effective for about two weeks and should then be removed.

Infected fractures treated with eradication of all infected material and in a second procedure with spongy bone transplantation and stable fixation will heal.

Intramedullary reaming combined with local mechanical cleaning and antibiotic therapy reduces the risk of relapse and reduces pain in chronic sclerosing osteomyelitis.

In patients with bacterial arthritis and delay in diagnosis or primary inappropriate antibiotic therapy, synovectomy can prevent joint destruction.

A joint prosthesis can be safely inserted with gentamicin cement after septic coxitis, provided primary anti-infectious therapy has been given.

Gentamicin cement continues to release GM in vivo for many years. After 30 days an average of 1 mg/day is available for antimicrobial action at the cement/tissue interface. Postulating a 1 mm thick tissue-layer surrounding the cement, approximately 67 ug would be available per cm^3 and day.

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Antibiotic containing bone cement beads in the treatment
of deep muscle and skeletal infections

by

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ANTIBIOTIC CONTAINING BONE CEMENT BEADS IN THE TREATMENT OF DEEP MUSCLE AND SKELETAL INFECTIONS

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Forty-eight cases of chronic osteomyelitis or bacterial arthritis operated on with eradication of infections lesions were randomly treated either by insertion of suction-irrigation drainage or by implantation of gentamicin beads. The average follow-up time was 2 years.

There was no difference in the recurrence rate between the two groups. The gentamicin treated patients were however more easily cared for as the suction-irrigation drainage required constant attention.

Local temporary treatment with gentamicin beads should be used in cases of deep gram-negative muscle and skeletal infections where it would otherwise be necessary to give toxic antibiotics.

Key words: bone cements; drainage; gentamicins; osteomyelitis

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During the past decade antibiotic containing bone cements have been successfully used both as a prophylaxis against infections in operations with joint replacements (Buchholz & Gartmann 1972, Gartenmann et al. 1973, Buchholz et al. 1977) and as a means of combating an established infection in revision of infected total hip arthroplasties (Buchholz et al. 1977, Carlsson et al. 1978). The cement has been shown to release antibiotics in such quantities *in vitro* and *in vivo* that the local concentrations exceeded the MIC values of most bacteria considered capable of causing skeletal infection (Wahlig et al. 1972, Gardner & Medcraft 1974, Picknell et al. 1977, Wahlig & Dingeldein 1978). Of the various types of bone cement now available Palacos^R has proved to be the most effective in releasing antibiotics (Gartenmann et al. 1973, Lindberg 1979).

On the basis of their experience in revisions of infected total hip arthroplasties, Voorhoeve & Stöhr (1973) treated 17 patients with chronic osteomyelitis by insertion of a gentamicin-polymethylmethacrylate plug. However, during an observation period of 20 months, five recurrences occurred. In order to increase the release of antibiotics, which occurs in proportion to the surface dimensions of the cement, Klemm (1976) introduced an antibiotic bone cement mixture in bead shape. The separate beads were left in place in the first cases operated upon but the technique was later modified so that 30 antibiotic beads were threaded on a twisted stainless steel string which permitted easy extraction. These antibiotic beads (Septopal, Merck, West Germany) have been used principally in deep subacute or acute soft tissue and skeletal infections (Klemm 1976).

The aim of the present study was to compare conventional treatment using suction-irrigation drainage with treatment by implantation of antibiotic bone cement beads in a series of patients with severe chronic osteomyelitis and bacterial arthritis.

MATERIAL

This study comprised 47 patients with 48 cases of chronic osteomyelitis or bacterial arthritis. All of them would otherwise have been treated with radical eradication of the infected tissue and insertion of a closed suction-irrigation drainage (Willenegger & Roth 1962). The indications for operation were an active secreting fistula, or severe pain at rest or repeated exacerbations. The series consisted of 32 men and 15 women aged 12–80 years with a mean age of 49 years.

The infection was hematogenous in five cases and post-traumatic after open fractures in six cases where no primary operations had been performed. Thirty-seven were postoperative infections of which 33 had had foreign material implanted.

The average duration of the disease was 10 years range (1–64 years). In 11 patients the disease had been present for more than 10 years.

The location of the infections is shown in Figure 1. Fourteen were located in a joint, the remaining 34 in the skeleton.

In a prospective study it was decided at random whether the patients would be treated with gentamicin beads or by suction-irrigation drainage. Chronic osteomyelitis and bacterial arthritis were equally distributed in the two groups. All of the patients had normal kidney function before operation.

BACTERIOLOGY

The bacteriologic cultures were classified as positive only if repeated samples taken from fistulas on several occasions showed growth of the same bacteria or if more than three out of five cultures taken during operation from various sites in the operation area showed identical bacteria (Lidgen et al. 1978). Deep biopsy cultures were taken from the infected tissue. If foreign material was present, the biopsies were taken from the adjacent tissue. To avoid contamination each piece of tissue was taken with a separate sterile forceps, put into a separate CO₂ tube, and im-

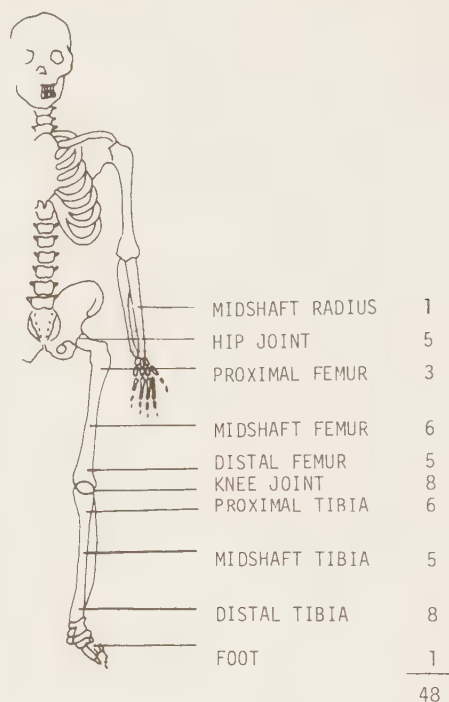


Figure 1. The localization in 48 cases of chronic osteomyelitis.

mediately taken to the bacteriologic laboratory for both anaerobic and aerobic cultures. The results are shown in Table 1. The most common bacteria found was *Staphylococcus aureus* but

Table 1. Results of bacteriological culture in 48 cases of chronic osteomyelitis

<i>Staphylococcus aureus</i>	20
<i>Staphylococcus epidermidis</i>	1
α -streptococci	1
β -streptococci	2
<i>Streptococcus faecalis</i>	2
<i>Escherichia coli</i>	2
<i>Pseudomonas pyocyanaea</i>	7
Anaerobic streptococci	1
Aerobic mixed infection	4
Anaerobic + aerobic	
mixed infection	6
Negative culture	2

seven out of 46 positive cultures showed growth of *Pseudomonas pyocyanea*.

METHODS

Forty-eight operations were performed on 47 patients, 23 of whom were treated with gentamicin beads and 25 by conventional methods. A complete eradication of the infectious lesion was aimed at in all cases.

All patients received systemic antibiotics after the culture specimens were taken. This antibiotic treatment was continued for an average of 7 months postoperatively. Seven cases from each group are currently undergoing treatment.

In some cases the treatment deviated in principle and will therefore be discussed further. Intramedullary reaming was performed in 14 cases in order to revitalize and revascularize the bone through improvement of the endosteal circulation (Lidgren & Törholm 1980). In one case an internal fixation was carried out with a Küntscher nail and in one with a Zickel nail. In seven cases external fixation according to Vidal-Adrey was used. In five cases of bacterial arthritis partial synovectomy was performed, four in the knee joint and one in the hip; in the latter case resection of the femoral head was also carried out. The foreign material was usually extracted, but in cases of unhealed fractures the fixation was retained until the fracture was healed.

To evaluate the extent of devitalized tissue intravital staining with Disulphine Blue (ICI Great Britain) was used in nine cases (Klemm 1976). This also facilitated the extirpation of all granulation tissue and sequestra. Disulphine Blue was given intravenously for 10 minutes in the operating theatre by the anesthesiologist 1 hour before operation. The Disulphine Blue disappeared within 2 to 3 days. No side-effects were observed.

The antibiotic beads used were 7 mm in diameter and had a weight of 0.2 grams. Each bead contained 7.5 mg gentamicin corresponding to 4.5 mg of gentamicin sulphate.

The beads were inserted into bone as well as into soft tissues. The remaining cavities were filled at operation with beads, the number varying from eight (36.0 mg gentamicin base) to 540 (2430 mg gentamicin base). The beads were left in position, usually with one bead outside the skin to facilitate removal which was done after 2 weeks (range 8–29 days) without the use of anesthetics. Three of the cases were operated on more than once and when the beads were removed a transplantation of cancellous bone was carried out. Measurement of the gentamicin concentration in

the serum, urine and blood was carried out in nine cases.

The average treatment time with closed suction-irrigation drainage was 4 days (range 2–7 days). The suction-irrigation period ended with 2 days of suction drainage only. Ten to fifteen liters of acetated Ringer's solution at body temperature and without antibiotic additive was heated in a blood-warming vessel and circulated continually throughout the operation area.

RESULTS

All patients were re-examined on average 24 months postoperatively (range 9–39 months). Two recurrences were noted in the group with gentamicin beads. One case had had an open fistula for more than 33 years and a poor condition of the skin in the lower leg. An attempt to move a skin flap was unsuccessful, the wound split open, and the fistulae recurred; however, after 9 months it was still free from the original strain of *Pseudomonas pyocyanea*. The other patient had a small persistent fistula which produced a drop or two of pus daily.

Four recurrences were noted in the group treated by suction-irrigation drainage. Two abscesses needed incision, one after 1 month, the other after 7 months. The original bacterial strain was cultured in both cases. In another patient the pain continued and a new fistula developed after 9 months. The fourth patient retained his fistula during the entire postoperative period, but the condition was painless. No significant difference between the two groups was found concerning the recurrence of the infection ($P > 0.05^{-1}$ Chi-square test).

Some difficulty was encountered in comparing the two groups in terms of the time spent in hospital and in bed, because of other injuries, and seven patients were not included in this calculation. The average length of time spent in hospital in the group treated with suction-irrigation drainage was 22 days of which 5 were spent in bed. The figures for the gentamicin group were 27 and 3 days, respectively.



Figure 2. Gentamicin concentrations in serum, wound secretion and urine after implantation of gentamicin – polymethylmethacrylate beads (mean 140 beads, range 18–540) in nine patients with chronic osteomyelitis.

Gentamicin concentrations were determined by G. Kahlmeter, Department of Medical Microbiology, Lund, Sweden, using a previously described agar well diffusion technique (Kahlmeter et al. 1978).

Twenty-two of the patients had unhealed fractures and chronic osteomyelitis. These fractures were all healed at re-examination. The gentamicin concentration in the wound secretion, blood and urine for the nine patients examined is shown in Figure 2.

Case report 1

An 18-year-old girl with a closed femoral fracture and a comminuted fracture of the tibial plateau. The patient was operated upon after 2 weeks with open reduction and fixation of the fracture of the tibial plateau by a screw and of the femoral fracture by a Küntschner nail after intramedullary reaming. Postoperatively the patient developed a hematoma, which was evacuated. After this a severe infection developed with growth of *Staphylococcus aureus*. In spite of treatment with antibiotics (cloxacillin, gentamicin, lincomycin in high doses), the patient's septic condition continued. On radiographic examination gas was noted in the soft tissues surrounding the femoral fracture. The patient was reoperated upon and an abscess was found communicating with the

fracture. Preoperative cultures showed no bacterial growth. After débridement, 60 gentamicin beads were inserted (Figure 3a). The patient was also treated with lincomycin parenterally and improved rapidly. After 3 weeks there was no sign of infection and the beads of which a couple were left outside the skin were extracted (Figure 4b).

Case report 2

A 34-year-old man with an infected tibial shaft fracture after primary fixation with an AO-plate.

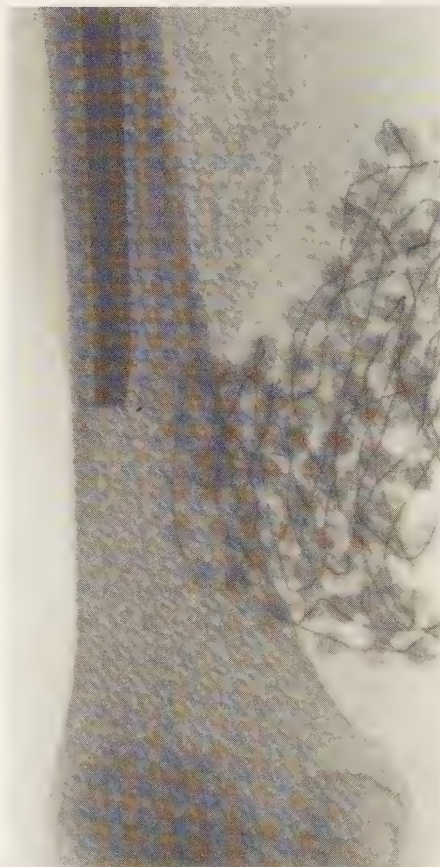


Figure 3a. Radiographic examination showing 60 gentamicin beads inserted into the cavity adjacent to the femoral fracture.

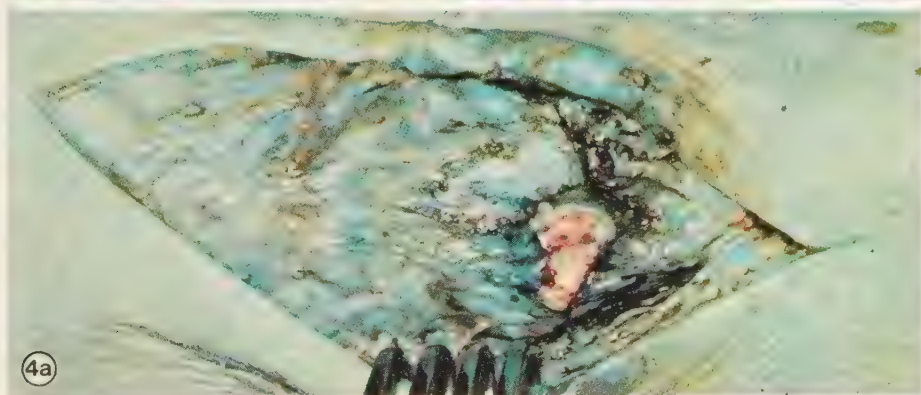


Figure 3b. The green colouring of a patient shown 1 hour after intravital staining with Disulphine Blue.

Figure 4a. The operating area is shown with a clearly visible white sequestrum.

Figure 4b. A couple of beads should be left outside the skin to facilitate extraction.

The plate had been removed after 5 months. The patient was treated with a plaster cast for 1 year but a fistulating infected non-union occurred. The patient was operated upon after intravital staining (Figure 3b) with radical eradication of infected soft tissue and necrotic bone (Figure 4a) and subsequent insertion of 18 gentamicin beads. The fracture was stabilized with the Vidal-Adrey apparatus. Transplantation of cancellous bone was carried out 4 weeks later and the patient was allowed to gradually take weight on the affected leg. The external fixation was abandoned after 3 months. The patient was given a below-knee brace (Sarmiento 1970) for an additional 3 months and he was allowed full weight-bearing. Eight months after the bone transplantation, the fracture was united.

DISCUSSION

Successful treatment with gentamicin beads in deep acute and subchronic infections of bone and soft tissue has been reported by Klemm (1976) and Jenny et al. (1977). The observation period in the present study was 24 months, too short a time to judge the healing results in chronic osteomyelitis, but there was no difference in the recurrence rate between our groups. There was no decrease in the time spent in the hospital but the patients treated with gentamicin beads spent about 2 days less in bed. The main advantage was that these patients were more easily cared for as the suction-irrigation drainage required constant attention and often caused difficulties (Asche 1978).

The majority of the infections in this study were caused by *Staphylococcus aureus* but in no less than 16 per cent (7/48) the responsible organism was *Pseudomonas pyocyanea*. Systemic treatment with toxic preparations could be avoided and concentration determinations in nine of the patients showed no measurable levels of gentamicin in the blood. This is in agreement with other reports (Wahlig et al. 1972, Wahlig & Dingeldein 1978). On the other hand, an accumulation of gentamicin could admittedly occur in the kidneys, since a significant quantity of gentamicin is excreted in the urine. A rapid

release *in vitro* as well as *in vivo* has earlier been shown, with a certain delay in the latter case (Picknell et al. 1977). There is little reason to leave the gentamicin beads longer than about 2 weeks, considering the rapid release of antibiotics found in this investigation, particularly during the first week. Moreover, the extraction of the beads may become difficult after more than 2 weeks because fibrous tissue grows in between the beads. Gentamicin is most important in gram-negative infections especially those caused by *Pseudomonas pyocyanea* but is also effective in *Staphylococcus aureus* infections and probably effects some anaerobic bacteria in the very high concentrations which are obtained initially. No development of resistance against gentamicin during treatment was noted in this investigation. There is reason, however, to direct treatment only against the infectious agent in local treatment. Experiments with other antibiotics added to bone cement show similar results (Voorhoeve & Stör 1973, Levin 1975, Picknell et al. 1977, Lindberg 1979).

Temporary treatment with gentamicin beads should thus be confined principally to cases of deep gram-negative muscle and skeletal infections where it is otherwise necessary to apply general treatment with toxic preparations. Tensionless sealing of the skin is a prerequisite for this method and if a large cavity remains, this can later be filled with cancellous bone or muscle.

ACKNOWLEDGEMENT

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II

Intramedullary reaming in chronic diaphyseal osteomyelitis:

A preliminary report

by

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Intramedullary Reaming in Chronic Diaphyseal Osteomyelitis:

A Preliminary Report

LARS LIDGREN, M.D., AND CARSTEN TÖRHOLM, M.D.

Patients with chronic osteomyelitis often have severe pain at rest and at weight-bearing. Fistulation makes the patient feel embarrassed, unclean and afraid of contaminating the environment. The purpose of this study was to improve the treatment of longstanding chronic osteomyelitis of diaphyseal bone by adding intramedullary reaming to conventional local eradication.

MATERIAL AND METHODS

The material comprised 18 cases of chronic diaphysary osteomyelitis in 17 patients (Table 1) with repeated exacerbations, fistulation or severe pain or both, all operated upon at the Department of Orthopaedic Surgery in Lund, Sweden, during 1974–78. All except four of the patients were operated upon by the authors. Fifteen of the patients were referred from another hospital. Thirteen were men and four women, aged 14–70 years with an average age of 45 years. The average duration of the disease was 19 years.

The etiology was hematogenous in three cases, and traumatic in 15, of whom eight had had foreign material implanted. The osteomyelitis was localized in nine cases to the tibia and in nine to the femur.

The local infectious lesion was first extirpated. Thereafter intramedullary reaming with a Küntscher drill was carried out from proximally

and distally to the osteomyelitic lesion through separate drill holes in the metaphyses. (See case report.) Reaming of the chronic osteomyelitis with an open marrow cavity was not difficult and the purpose in these cases was primarily to clean out the medullary cavity. However, in sclerotic obliterated marrow cavities the operation was laborious. As a rule, a sharp guide had to be forced through the sclerotic bone before a 9-mm drill could be used. This was then changed to a blunt guide for reaming up to 11–13 mm for the tibia and 15–18 mm for the femur.

In addition to the reaming, the following conventional treatment was performed. Nine cases were treated with closed intramedullary suction-irrigation drainage (Table 1) with 10–15 liters of acetated Ringer's solution, without antibiotic addition, daily for about five days (range 3–9 days). The solution was warmed to body temperature through a blood-warming vessel. The irrigation drainage was followed by about two days of suction drainage only.¹

In four patients with osteomyelitis the fractures were not healed. Three had a new Küntscher nail and one a Zickel nail.² These patients had only closed-drainage treatment. When the fractures were healed the osteosynthetic material was removed.

In five patients gentamicin–polymethylmethacrylate beads (Merck, Darmstadt, Germany) were implanted into the marrow cavity.³ These beads, in strings of 30 threaded on stainless steel, contained 7.5 mg gentamicin sulfate per bead, and were used for an average of 13 days (range 7–16 days). The number of implanted beads varied from 30 to 88. In most instances, one of the beads was left outside the skin so that the string could be extracted without the use of anesthetics. The patients were confined to bed for an average of four days (range

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TABLE 1. Summary of 18 Patients with Chronic Diaphysary Osteomyelitis

Age	Sex	Etiology	Duration of Infection (years)	Treatment		Duration of Follow-up (months)	Outcome
				Surgical	Antibiotic		
33	M	Post-operative	2	Negative cultures	Intramedullary reaming of tibia Kuntscher nail closed drainage	Cloxacillin 0.5 g × 4 in 6 months	53 No recurrence
58	M	Post-operative	1	<i>E. coli</i> <i>Streptococcus faecalis</i>	Intramedullary reaming of tibia Intramedullary suction-irrigation drainage 9 days	Cloxacillin 0.5 g × 4 in 14 months	44 No recurrence
26	F	Post-operative	2	<i>E. coli</i>	Intramedullary reaming of femur Intramedullary suction-irrigation drainage 5 days	Cephalothin 0.75 g × 3 in 2 months	42 No recurrence
62	M	Post-operative	51	<i>Staphylococcus albus</i>	Intramedullary reaming of femur Intramedullary suction-irrigation drainage 5 days	Cloxacillin 1 g × 3 in 22 months	36 No recurrence
66	F	Post-operative	64	<i>Staphylococcus aureus</i>	Intramedullary reaming of tibia Intramedullary suction-irrigation drainage 6 days	Cloxacillin 1 g × 3 in 7 months	33 No recurrence
70	F	Post-operative	1	<i>Enterobacter aerogenes</i> <i>Peptococcus magnus</i>	Intramedullary reaming of femur 88 gentamicin-poly-methylmethacrylate beads 12 days	Cephalothin 1 g × 4 in 8 months	31 No recurrence

39	M	Post-operative	4	<i>Staphylococcus aureus</i>	Intramedullary reaming of femur Intramedullary suction-irrigation drainage 7 days	Cloxacillin 1 g $\times$ 4 in 29 months, is still being treated	29	Soft-tissue abscess 4 weeks after the operation with the same bacteria later; no recurrence
52	M	Post-traumatic	32	<i>Staphylococcus aureus</i>	Intramedullary reaming of tibia 30 gentamicin-poly-methylmethacrylate beads 14 days	Cephalothin 1 g $\times$ 4 in 10 months	25	No recurrence
66	F	Post-operative	1	Negative cultures	Intramedullary reaming of femur; Zickel nail; closed drainage	Cloxacillin 1 g $\times$ 4 in 3 months	25	No recurrence
41	M	Post-traumatic	20	<i>Staphylococcus aureus</i>	Intramedullary reaming of tibia 30 gentamicin-poly-methylmethacrylate beads 16 days	Cloxacillin 1 g $\times$ 4 in 5 months	24	No recurrence
69	M	Hematogenic	58	<i>Staphylococcus aureus</i>	Intramedullary reaming of tibia Intramedullary suction-irrigation drainage 4 days	Cloxacillin 1 g $\times$ 4 in 23 months, is still being treated	23	No recurrence
69	M	Hematogenic	58	<i>Staphylococcus aureus</i>	Intramedullary reaming of femur Intramedullary suction-irrigation drainage 4 days	Cloxacillin 1 g $\times$ 4 in 23 months, is still being treated	23	The fistula did not heal, but it was reduced
39	M	Post-operative	21	<i>Staphylococcus aureus</i> <i>Streptococcus faecalis</i>	Intramedullary reaming of femur Intramedullary suction-irrigation drainage 3 days	Cloxacillin 1 g $\times$ 3 in 10 months	23	No recurrence

TABLE 1. (Continued)

Age	Sex	Etiology	Duration of Infection (years)	Treatment			Duration of Follow-up (months)	Outcome
				Microorganism	Surgical	Antibiotic		
18	M	Post-traumatic	2	<i>Staphylococcus aureus</i>	Intramedullary reaming of tibia Küntscher nail closed drainage	Cloxacillin 0.5 g $\times$ 4 in 6 months	21	No recurrence
20	M	Post-operative	1	<i>Staphylococcus aureus</i>	Intramedullary reaming of femur Intramedullary suction-irrigation drainage 7 days	Cloxacillin 1.5 g $\times$ 3 in 6 months	18	No recurrence
52	M	Post-traumatic	13	<i>Staphylococcus aureus</i>	Intramedullary reaming of tibia 30 gentamicinpoly-methylmethacrylate beads 14 days	Cloxacillin 1 g $\times$ 4 in 19 months	19	No recurrence
17	M	Post-traumatic	2	<i>Staphylococcus aureus</i>	Intramedullary reaming of tibia Küntscher nail; closed drainage	Cloxacillin 1 g $\times$ 4 in 17 months, is still being treated	17	No recurrence
14	M	Hemato-genic	10	Negative cultures	Intramedullary reaming of femur 30 gentamicinpoly-methylmethacrylate beads 7 days	Cloxacillin 0.5 g $\times$ 3 in 3 months	16	No recurrence Fracture of the femur at the proximal drill hole four weeks postoperatively which healed on conservative treatment in 3 months

1-9 days) and were allowed weight-bearing after about two weeks.

The bacteriologic cultures were considered positive only if samples taken from the fistula on several occasions preoperatively showed growth of the same bacteria or if more than three of five cultures obtained at operation from various sites in the operative area showed identical bacteria.^{7,9} All patients were without antibiotics at least six weeks before the operation. After the culture specimens were taken, all patients received antibiotics intravenously during the operation. Postoperative antibiotics were administered perorally for an average of ten months according to the pattern of resistance. Cloxacillin was given in 15 cases and cephalothin in three. Three patients are still being treated.

RESULTS

The postoperative observation period was 28 months (range 16-53 months) (Table 1). Two patients had recurrences. One fistula did not heal but the patient was relieved of his pain. The other patient had a soft-tissue abscess with growth of the same bacteria four weeks after operation. The abscess was incised and the patient was free of symptoms 29 months after the operation. The remaining 16 patients did not show any signs of recurrence.

Nine of the patients had marked pain at rest and at weight-bearing before the operation. Eight of these became free from pain. One had only slight pain at weight-bearing, compared with severe pain even at rest before the operation.

Eight of 15 patients with recurring fistulation had severe psychological problems before operation, believing that they were unhygienic and guilty of contaminating the environment. They felt isolated and thought that people around them were fearful of being infected with "hospital contagion." All of the patients were markedly relieved after the operation. Three patients did not have any psychological problems but they had all had the disease for a very long time (20, 51 and 58 years).

There were no other complications except for an oblique fracture of the femur through

the proximal drill hole in a 14-year-old boy who sustained a minor trauma four weeks postoperatively. The fracture was treated by traction and cast-brace and healed uneventfully.

CASE REPORT

A 66-year-old woman had had a traumatic osteomyelitis of the tibia at two years of age. The patient was not allowed weight-bearing until the age of 7. During the first 30 years she had several recurrences, and two local operations were performed. She was without any symptoms for another 20 years, but for the last 10 years she had continued pain, initially at weight-bearing, and for the last three years she had also had severe pain at rest. For the last ten years there had been fistulation. Repeated cultures from the fistula had shown growth of *Staphylococcus aureus*. Long-term treatment had reduced the secretion from the fistula but had not had any effect on the pain. When the patient was referred to our department, the radiographic examination showed sclerotic changes in the tibia, especially in the middle part (Fig. 1). No sequestras were found. The patient had at this time a skin lesion of 2 x 3 cm with visible bone. The local infectious lesion was first extirpated. At operation intramedullary reaming of the tibia was carried out from proximal and distal to the lesion through separate drill holes in the metaphyses (Fig. 2). A sharp guide was forced through the sclerotic bone and changed to a blunt guide before reaming, starting with 9 mm drilling, up to 13 mm were performed. A closed intramedullary suction-irrigation drainage was used for five days, flushing the bone with about 10 liters of acetated Ringer's solution daily. Two days of suction only followed before drainage was removed. The patient was given cephalothin 1 g four times a day peroperatively and continuously for six months. Cultures during the operation were negative. Postoperatively, the patient was immediately relieved of her pain at rest, and six weeks later she started weight-bearing without any pain. Three years later there is no recurrence and the patient is free of symptoms.

DISCUSSION

The difficulties in treating chronic osteomyelitis are well illustrated by the multitude of methods to be found in the literature. Burning wood (1500-800 B.C.),¹¹ iodine



FIG. 1. (Left) Radiographic examination showing chronic osteomyelitis of the left tibia with sclerotic changes, especially in the middle part. **FIG. 2. (Right)** Radiographic examination after intramedullary Küntscher reaming (13 mm). The proximal entrance is just above the tibial tubercle. The suction-irrigation drainage in the medullary cavity is shown.

pellet fillings,¹⁴ and antibiotic whipped-blood mixture have been used in osteomyelitis cavities.¹⁶ The combination of radical surgery and antibiotic therapy in the management of most cases of posttraumatic osteomyelitis is currently accepted.¹³

Long-term antibiotic treatment of chronic osteomyelitis without sequestrations may diminish pain and even cause healing of fistulae. About one fifth of such cases, however, have frequent exacerbations that cause continuous pain at rest, which disturbs sleep, and occasional fistulation.⁵

Before this study was undertaken we did not fully understand that the fistulation caused by the osteomyelitis constituted

such a psychological strain for the patients. In our series this was true for no less than half of the patients, who were markedly relieved after the operation.

The risk of malignancy, *i.e.*, that the disease may develop into squamous epithelial cancer, is slight (0.5%) but increases with the length of the fistulation period.⁸ This should also encourage a more active treatment in cases of long-term chronic osteomyelitis.

In chronic diaphysary osteomyelitis, severely sclerotic, poorly vascularized bone is often found.^{2,15} Pain at rest in these cases can be interpreted as a sign of increased intraosseous pressure.^{1,10} In this study not only conventional local eradication was carried out, but also intramedullary reaming, with the purpose of diminishing the intraosseous pressure and revascularizing the bone, thereby improving the endosteal circulation.¹² Intramedullary reaming in a severely sclerotic bone is not an easy operation, but in the present investigation it did not cause complications other than a fracture three weeks postoperatively.

Intramedullary reaming had a prompt effect in nine cases with severe pain. Even though we do not know how long this effect will last, this procedure might well be justified in these severely afflicted patients.

The method is, however, still under evaluation and does not yet offer any advantages over standard techniques with, for instance, sequestrectomy and saucerization. All the patients had, however, been operated upon before with standard techniques, though not by the authors, most of them several times with almost immediate recurrences and no pain relief.

The good results of the treatment with only two recurrences are encouraging and indicate that the usual treatment with local extirpation and antibiotics⁴ completed with intramedullary reaming might improve the healing of osteomyelitis, although the

series is small and the average follow-up time was only 28 months.

SUMMARY

Eighteen cases (17 patients) of chronic diaphyseal osteomyelitis with repeated exacerbations have been operated on by intramedullary reaming in addition to the conventional local surgery and antibiotic therapy. Nine patients with severe pain at rest were promptly relieved by the operation. The observation time was 28 months. In one case the fistula persists. The remaining patients have "healed." The average duration of the disease was 19 years.

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III

Synovectomy in bacterial arthritis

by

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SYNOVECTOMY IN BACTERIAL ARTHRITIS

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Twenty patients with bacterial arthritis with either delay in diagnosis or no response to treatment are presented. Synovectomy, even when performed after 5 days and up to 4 weeks later, could prevent joint destruction in the knee but not in the hip. The average follow-up time was 5 (2–9) years.

Key words: bacterial arthritis; hip; knee; synovectomy

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Joint destruction and even mortality have been reported in bacterial arthritis during the last 10 years, showing that there are still difficulties with diagnosis and treatment (Howard et al. 1976, Kelly et al. 1970, Lidgren & Lindberg 1973, Newman 1976, Sharp et al. 1979).

The aim of this investigation is to report the results of synovectomy in 20 consecutive patients with bacterial arthritis with either delay in diagnosis or no response to early antibiotic treatment.

PATIENTS AND METHODS

During the period 1973–1980, 20 patients with bacterial arthritis were synovectomized. Seventeen of these operations were performed at the Department of Orthopaedic Surgery, Lund, and three in other hospitals after consultation. This is one third of all patients treated for bacterial arthritis during the period. All patients with foreign material in the joint have been excluded from this study.

There were 14 men and six women, with an average age of 42 years (range, 5 weeks to 72 years). Seven of the patients were younger than 16 years (Table 1). The infection was haematogenous in nine cases and post-traumatic or postoperative in 11 cases (Table 1).

The criteria for infection in these patients included at least one of the following:

- 1) Positive culture taken by sterile aspiration.
- 2) Positive culture biopsy from the synovium.
- 3) Radiographic changes showing osteomyelitis.
- 4) Fistulation from the joint.

Three patients had negative cultures but were treated with penicillin before admission. Two of these had radiographic osteomyelitic changes (Case 5, 13) and the third had an infected wound with communication to the knee joint and severe secretion of pus (Case 15). Two patients had positive culture from synovial tissue biopsies (*Bacteroides* and *Propionibacterium acnes*) but negative cultures from aspirated material (Case 2, 14).

Antibiotic treatment was, in most cases, started after joint fluid analysis without waiting for the result of culture (Griffin 1979, Lloyd-Roberts 1979, Nade 1977, Petersen et al. 1980, Russell & Ansell 1972). The antibiotic treatment given during the period was either cefuroxime or a combination of ampicillin and cloxacillin parenterally for 1–2 weeks in adequate doses, as well as orally for an average of 4 months (range 1–8 months).

In all coxitis or postoperative infections, an arthrotomy was performed immediately after diagnosis. Haematogenous bacterial arthritis in other joints was treated initially by repeated aspiration and irrigation of the joint and if the symptoms had not decreased within 1–2 days or if pus was found, an arthrotomy, as above, was performed.

For coxitis, we used a dorsal approach and the femoral head was not luxated. Most of the pannus could be removed by rotating the femoral head. The joint was drained and flushed several times during the operation

SYNOVECTOMY IN BACTERIAL ARTHRITIS

Table 1. Twenty patients with bacterial arthritis operated with synovectomy

Case	Sex	Age (years)	Locali- sation	Aetiology	Duration of infection before synovectomy	Bacterial culture	Follow-up		
							Duration (Months)	ESR Results	
1	M	22	Knee	Haemato- genous	6 months	<i>Mycobacterium tuberculosis</i> Human type	107	8	Good
2	M	14	Hip	Haemato- genous	5 months	<i>Bacteroides</i>	101	6	Poor. 10-45 de- grees flexion. No pain.
3	F	5 weeks	Hip	Haemato- genous	9 days	<i>Staph. aureus</i>	100	5	Poor. Positive Trendelenburg. 20-135 degrees of flexion. Ab- duction 30 de- grees. Rotation 20 degrees 4 cm shortening. No pain.
4	F	5	Hip	Haemato- genous	3 days	<i>Staph. aureus</i>	100	5	Good
5	M	9	Knee	Post- traumatic	13 days	Negative	93	3	Good
6	F	4	Hip	Haemato- genous	3 days	<i>Staph. aureus</i>	92	6	Good
7	M	25	Knee	Postop. sha- ving of the patella	7 days	<i>Staph. aureus</i>	76	3	Good
8	M	73	Hip	Haemato- genous	1.5 years	<i>Staph. aureus</i>	75	2	Poor. No re- currence. Total hip arthroplasty.
9	M	9	Knee	Haemato- genous	18 days	<i>Staph. aureus</i>	70	7	Good
10	M	23	Knee	Postop. suture of an- terior cruciate ligament	14 days	<i>Staph. aureus</i>	64	5	Good
11	M	53	Knee	Postop. extraction of Ender nails	28 days	<i>Staph. aureus</i>	52	5	Good
12	M	38	Knee	Postop. menisc- ectomy	22 days	<i>β-streptococci</i>	48	7	Good
13	F	3	Knee	Haemato- genous	10 days	Negative	47	6	Good
14	M	60	Hip	Haemato- genous	3 months	<i>Propioni- bacterium acnes</i>	46	40	Poor. No re- currence. Total hip arthroplasty.
15	M	8	Knee	Post- traumatic	11 days	Negative	35	6	Good

Case	Sex	Age (years)	Locali- sation	Aetiology	Duration of infection before synovectomy	Bacterial culture	Follow-up	
							Duration (Months)	ESR Results
16	M	24	Knee	Postop. suture of an- terior cruciate ligament	4 days	<i>Staph. aureus</i>	32	2 Good
17	F	37	Knee	Postop. open reduction screw fixation of lateral tibial con- dylar fracture	17 days	<i>Staph. aureus</i> <i>Klebsiella</i>	24	3 Fair. 10–120 degrees flexion. Slight pain at weight bearing
18	M	79	Knee	Post- operative arthrography	7 days	<i>Staph. aureus</i>	23	5 Good
19	F	60	Knee	Postop. wire cerclage of patella fracture	7 days	<i>Staph. aureus</i>	23	20 Fair. 0–130 de- grees flexion. Slight pain at weight bearing
20	M	43	Knee	Postop. extraction of AO condyle plate	22 days	<i>Staph. aureus</i>	22	5 Good

ESR = erythrocyte sedimentation rate.

with physiological saline, a thick drainage tube was left in the joint cavity and the wound was closed with a few sutures. In two patients with considerable delay in diagnosis and treatment (3 months and 18 months) (Case 14, 8), the joint destruction was so advanced that femoral head resection and synovectomy were performed, followed by a Girdlestone period and then a total hip arthroplasty with gentamicin cement (Carlsson et al. 1978).

For the knee joint, a conventional para-patellar medial incision with luxation of the patella was used. Where pannus was growing over the cartilage, this was thoroughly cleansed away. All granulation tissue around the collateral and crucial ligaments was thoroughly removed. In cases of underlying bone destruction, the osteomyelitis was thoroughly eradicated. The operation, when possible, was performed in a bloodless field. Continuous suction irrigation drainage with 10–15 l Ringer acetate solution at body temperature was instituted for 3–8 days, followed by 2 days of suction (Hedström et al. 1980). The joint was immobilized for the first postoperative week. Active mo-

tion was then started, followed by gradual weight bearing after 6 weeks. If the flexion of the knee joint after 2 weeks of active training was less than 90 degrees, a mobilization in general anaesthesia was performed. This was done for seven patients; one patient was mobilized twice, and one three times.

The patients were followed clinically and radiographically for an average of 5 years (range 1.8–8.9 years). The erythrocyte sedimentation rate (ESR) was taken. For comparison, a radiogram was taken of the contralateral joint. In patients treated for arthritis of the knee, varus and valgus stress diagrams were taken. At the clinical investigation, pain at rest or weight bearing, joint motion, and working capacity or daily activity were recorded.

The patients were graded into three groups:

Good: Patients with no pain, normal motion, normal radiogram and normal daily activity.

Fair: Radiogram showing narrowing grade 2 (according to Ahlbäck 1968), slight pain at weight bearing, and slight limitation of mobility.

Poor: All remaining patients.

RESULTS

At follow-up all patients had ESR below 20 mm, except one who had classical rheumatoid arthritis (ESR 40 mm). There have been no recurrences of infection. The results of the treatment of various patients are shown in Table 1, and the results related to the delay in treatment in Table 2.

Two patients in the second group (Table 2) with an average delay of 15 days, both women, had at the same time a fracture of the patella and the lateral tibial condyle, respectively. These are the only two patients rated "fair". In the last group, with more than 4 weeks of delay, one patient had symptoms for 6 months and synovial tuberculosis. Eight years later, he had a normal knee joint, clinically and radiographically. The three other patients in the last group had advanced bone destruction after coxitis. Two were treated with resection of the femoral head and later had a successful total hip arthroplasty. The third patient had severe destruction of the hip with a motion of 10–45 degrees in extension flexion but no pain. In Table 3, results regarding mortality and joint destruction are compared with other materials from the last 12-year period.

Table 2. Follow-up result related to delay in treatment for 20 patients with bacterial arthritis operated with synovectomy

Group	Delay in treatment		Follow-up		
	Days	Mean duration	Hip	Knee	Total *
I	0–5	3	2 good	1 good	3
II	6–28	21	1 poor	12 < 10 good 2 fair	13
III	>28	180	3 poor	1 good	4
Total			6	14	20

CASE REPORT

A 9-year-old boy (Table 1) (Case 9) was admitted 5 days after start of symptoms, with fever and pain in the right knee. Cultures from the joint fluid and blood showed growth of a non-resistant *Staphylococcus aureus*. Initial treatment started with cloxacillin 0.8 g four times daily. Synovial fluid was aspirated repeatedly but the pain was only slightly reduced and the patient still had a temperature between 38 and 39°C. Because of the persistent symptoms a synovectomy was performed

Table 3. Results of treatment reported by other authors

Authors	Publication year	Follow-up years	Number of patients	Number of joints	Results in survivors		
					Good* joints	Poor** joints	Death no. of patients
Kelly et al.	1970	2–10	78	67	16	51	12
Paterson	1970	2–9	96	96	70	26	0
Russell & Ansell	1972	1–10	28	46	34	12	2
Lidgren & Lindberg	1973	6	21	22	11	11	0
Goldenberg & Cohen	1976	3–10	59	55	35	20	5
Gérard et al.	1977		26	26	19	7	0
Wiley & Fraser	1979	1–4	50	56	41	15	0
Newman	1980	7	134	124	87	37	1
Rosenthal et al.	1980	2–8	63	64	32	32	5
Mielants et al.	1982	4	30	22	15	7	0
Total			585	582	355 (61%)		25 (4.3%)

* The patients in this group are classified according to the criteria of each author. All other patients (fair and poor) are in the poor group.

** The patients who died are not included.

on the 18th day after onset. Five cultures from the synovial tissue showed growth of *Staphylococcus aureus*. The patient improved dramatically, fever dropped, and after a week active motion was started. The antibiotic treatment was continued with oral fusidic acid and penicillin for 3 months. Two weeks after the synovectomy a mobilization of the knee in general anaesthesia was performed. At follow-up 6 years later he had no pain, full flexion and a normal radiogram.

DISCUSSION

In 1876, Thomas reported that aspiration of an infected joint by means of fluctuation could prevent cartilage destruction. Synovectomy was described as early as 1879 by Volkmann for synovial tuberculosis. Later investigations confirmed the good results of synovectomy for tuberculous arthritis (Wilkinson 1962). In the last decade, many investigations have shown that bacterial arthritis has to be treated intensively with antibiotics within 24–48 h after onset of symptoms, or irreversible joint cartilage damage will result (Goldenberg & Cohen 1976, Ho & Su 1982, Howard et al. 1976, Paterson 1970). High joint pressure and/or enzymatic degradation are the main reasons for the cartilage destruction (Fraser 1981, Paterson 1978, Salvati 1979). Therefore early antibiotic treatment and drainage with irrigation in order to reduce pressure and flush the joint are important (Lloyd-Roberts 1979, Wiley & Fraser 1979). However, in spite of these treatment principles, secondary joint changes have been known to develop and the sepsis may even lead to mortality (Griffin 1979, Kelly et al. 1970, Newman 1976, Russell & Ansell 1972, Sharp et al. 1979). The hip joint especially is very sensitive and many authors have recommended drainage within the first few days (Griffin 1979, Howard et al. 1976, Kelly et al. 1970, Lloyd-Roberts 1979, Nade 1977, Newman 1976, Paterson 1970). We found that synovectomy in bacterial arthritis as indicated by Gerard et al. (1977), even performed after 5 days and up to 4 weeks later, could prevent secondary joint destruction in the knee but not in the hip (Case 1) (Table 2). The results were also better in comparison with other published materials where synovectomy was not performed (Table 3).

As in other investigations (Ho & Su 1982, Paterson 1970), no complications developed in the patients who were treated within 5 days (Table 2). None of our patients treated with aspiration and antibiotic treatment alone are included in this study. If the patients came later with bone destruction, there was often no possibility of restoring the anatomy. It is, however, important to arrest and eradicate the infection for later reconstructive arthroplastic surgery (Table 1).

Low-virulent haematogenous anaerobic infections in joints without foreign material are rare and often missed (Lidgren et al. 1978). Two of our patients were treated for 3 and 5 months (Table 1) before diagnosis. Cultures from synovial biopsy gave growth of anaerobic bacteria in two of our patients (No 2, 14) with initial negative cultures. Other reports also showed that although repeated cultures from the joint fluid are negative, the patient can still have bacterial arthritis (Nade 1977, Petersen et al. 1980, Wiley & Fraser 1979). If there is a clinical suspicion of bacterial arthritis verified by the joint fluid analysis (Griffin 1979, Parker 1977), intensive antibiotic treatment and eventually operation should not be delayed.

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IV

Total hip replacement with gentamicin bone-cement after septic
arthritis

by

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INTRODUCTION

A septic arthritis often destroys the joint and gives rise to an osteomyelitis in the adjacent bone. Even in presumably healed cases there is a risk of reactivation of a quiescent bone infection, hence the hitherto restrictive attitude towards total hip replacement in such cases.¹⁰ However, the successful use of gentamicin-containing bone cement for exchange operations of infected total hip replacements^{3,6,7,11} indicated that the same principles could probably be applied to cases of septic arthritis. The purpose of this retrospective study was to present a series of total hip replacements using gentamicin-containing bone cement after a recent or past history of septic arthritis.

MATERIAL AND METHODS

The operations were performed at the University Departments of Orthopaedics in Lund and Malmö and at the Department of Orthopaedics in Gävle.

The material consists of 24 patients (Table 1) 14 women and 10 men with septic coxitis or infected hemiarthroplasty consecutively operated on with total hip replacement and gentamicin-containing bone cement between October 1975 and July 1980. Fourteen of the cases were referred to the participating hospitals after primary treatment in other hospitals.

The age at the time of the total hip replacement averaged 63 years (28-83). In 20 cases the infections were postoperative: nailing of a femoral neck fracture (16), uncemented hemiarthroplasty (3), and open fixation of an acetabular fracture (1). In the remaining four the infection was hematogenous. Tuberculous arthritis was not included.

The diagnosis of the infection

In all 24 cases there was a history of fever, pain and elevated ESR. The radiographic findings were in accordance with a septic arthritis with total destruction of the joint cartilage, demineralization, partial bone destruction, and subluxation or dislocation of the femoral head.¹ In the three cases with hemiarthroplasty there was subsidence and protrusion of the prosthesis, and progressive destruction of the bone surrounding the prosthesis. In the 20 cases of postoperative infection there had been local signs of infection; redness, swelling, and drainage from the wound. In 16 of these 20 cases local abscesses had developed, in 14 followed by fistulation. In two cases a sinus was present at the time of the total hip replacement.

In all cases positive bacteriological cultures had been obtained; in 11 (No 5, 6, 7, 9, 11, 13, 17, 20, 21, 23, 24) from abscesses, in two (No 8, 22) at extraction of hemiarthroplasties, in five (No 10, 12, 16, 18, 19) at revision of the hip for infected tissue, in two (No 14, 15) at needle aspiration from the joint and in three cases (No 1, 3, 4) from biopsies at the total hip surgery. In the remaining case (No 2) *E.coli* was cultured both before and at the total hip surgery. The results of the cultures are presented in Table 1.

Surgical treatment

The prostheses used were of the following designs; Lubinus 10, Charnley 8, Brunswik 6. The interval between the time of the diagnosis of the infection and the total hip arthroplasty averaged 17 months (range 3-67).

In 16 cases the total hip replacement was performed without any other prior surgical treatment than drainage of an abscess or extraction of the osteosynthetic material. After debridement of the infected tissue the total hip prosthesis was implanted with the use

Table 1

Case#	Sex	Age	Diagnosis	Duration of inf. months	Microorganisms		Antibiotic after revision	Sinus at THR	ESR		Follow-up				
					Preop	Intraop.			At the time of diagnosis	Preop.	Follow-up	Months postop.	Pat. category	Hip score	
Group I	1	F	61	Femoral neck fracture	36	Neg.	**Peptococcus magnus prevotii	Cloxacillin 1g x 4 for 1 week. Cefalexine 1g x 4 for 6 months	Yes	65	60	6	81	A	6-4-4
	2	M	37	Femoral neck fracture	22	E. coli	**E. coli	Cloxacillin 1g x 4 for 1 week. Trimetoprim + sulfa-metoxazol 6 months	No	97	6	5	46	A	5-5-5
	3	F	80	Moore prosthesis	21	Neg.	**S. haemolytic streptococcus group B	Doxycycline 100 mg x 1 for 3 days. Fluoximetylpenicillin 0.8g x 4 for 6 months	No	128	45	22	34	C*	6-4-3
Group II	4	M	68	Femoral neck fracture	6	Neg.	**Streptococcus viridans	Cloxacillin 1g x 4 for 3 months	No	112	70	11	20	A	6-5-5
	5	F	83	Femoral neck fracture	3	Staph.	Neg. aureus	Flucloxacillin 1g x 4 for 3 months	Yes	80	57	23	46	A	6-6-6
	6	M	45	Acetabular fracture operated	14	Staph. aureus + Ps pyocyanea	Neg.	Doxycycline 100 mg x 1 for 2.5 months	No	62	31	9	95	A	5-6-4
Group III	7	M	70	Femoral neck fracture	10	Staph. aureus	Neg.	Dicloxacillin 1g x 4 for 6.5 months	No	122	65	10	89	A	6-5-5
	8	F	62	Moore prosthesis	67	Staph. aureus	Neg.	Cloxacillin 1g x 4 for 6 months	No	84	32	25	87	B	5-4-2
	9	F	69	Femoral neck fracture	21	Staph. aureus	Neg.	Cloxacillin 1g x 4 for 3 days. 1g x 4 Cefalexine 1g x 4 for 3.5 months	No	95	42	15	83	B	6-4-5
Group IV	10	M	74	Hemotogenous colitis	13	Staph. aureus	Neg.	Fusidine acid 0.5g x 3 for 6 months	No	143	42	9	74	A	6-6-4
	11	F	51	Femoral neck fracture	24	Staph. aureus	Neg.	Cloxacillin 1g x 4 for 8 months	No	110	51	8	69	A	6-6-4
	12	M	58	Femoral neck fracture	19	Proteus morganii + S. haemolytic streptococcus group B	Neg.	Cloxacillin 1g x 4 for 1 week. Flucloxacillin 1g x 3 for 6 months	No	65	43	5	50	A	6-5-4

Group III	13	F	74	Femoral neck fracture	4	Staph. aureus	Neg.	Cloxacillin 1g x 4 for 6 months	No	60	13	13	76	A	5-4-4
	14	M	64	Hematogenous coxitis	26	Staph. epidermidis	Neg.	Cloxacillin 1g x 4 for 6 months	No	70	7	10	68	C	5-3-6
	15	M	28	Hematogenous coxitis	32	Staph. aureus	Neg.	Clindamycin 0.3g x 4 for 3 months	No	104	2	7	59	A	6-6-6
	16	F	83	Femoral neck fracture	4	**Staph. epidermidis	Neg.	Flucloxacillin 0.5g x 4 for 1.5 months	No	102	19	19	57	C	5-2-6
	17	F	66	Femoral neck fracture	12	Staph. aureus	Neg.	Cloxacillin 1g x 4 for 3 months	No	105	20	20	53	A	5-4-5
	18	M	60	Femoral neck fracture	13	**Bacillus subtilis	Neg.	Cloxacillin 1g x 4 for 3 weeks Cefalexine 0.5g x 4 for 4 months	No	123	15	4	48	B	6-3-5
	19	F	50	Femoral neck fracture	7	**Staph. epidermidis	Neg.	Cloxacillin 1g x 4 + Clindamycin 300 mg x 3 for 2 months	No	104	10	10	43	A	6-6-6
	20	M	56	Femoral neck fracture	5	Staph. aureus	Neg.	Cloxacillin 1g x 4 for 3 months	No	55	30	35	85†	C*	6-4-5
	21	F	75	Femoral neck fracture	14	Staph. aureus	Neg.	Dicloxacillin 1g x 3 for 3 months	No	116	50	36	64	C*	5-4-5
	22	F	66	Moore prosthesis	26	Proteus morganii	Neg.	Cloxacillin 1g x 4 + Clindamycin 300 mg x 3 for 7.5 months	No	60	38	14	64	C*	6-1-5
	23	F	64	Femoral neck fracture	13	Staph. aureus	Neg.	Cloxacillin 1g x 4 for 6 months	No	110	90	31	64	C*	6-4-5
	24	F	56	Hematogenous coxitis	11	Staph. aureus	Neg.	Cefalexine 1g x 3 for 1 week Lincomycin 1g x 3 for 6 months	No	100	54	30	41†	C*	5-3-4

The ESR was determined according to Westergren, normal values according to Böttiger and Swedberg⁴ are for men below 50 years 0-13 mm, over 50 years 0-19 mm and for women below 50 years 0-21 mm, over 50 years 0-28 mm.

* Patient with rheumatoid arthritis

** This bacteria was positive in 5/5 tissue samples, according to Kamme and Lindberg¹³

† Ad mortem

of gentamicin-containing bone cement*

In three cases (No 12, 18, 19) all infected tissue was first removed, the wound filled with gentamicin PMMA beads** and primary sutured. After four weeks the beads were removed and a total hip prosthesis implanted with the use of gentamicin-containing bone cement.

The remaining five patients had been subjected to varying forms of surgical treatment at other hospitals before they were referred to us. In three cases (No 10, 15, 16) suction-irrigation drainage had been applied. The total hip replacement had been performed 13, 32 and 3 months thereafter. The last two hips (No 8, 22) were uncemented hemiarthroplasties replaced by a total hip prosthesis 7 and 39 months after extraction, respectively.

Antibiotic treatment

In this retrospective study an attempt was made to evaluate the antibiotic treatment prescribed since the time of the diagnosis of the infection. In six cases long-term treatment with isoxazolylin-penicillin was given between 4 months and 2 years (4, 6 and 9 months, 1, 1½ and 2 years). In two of them cephalaxine was given for 4 months and 1 year, respectively, in one clindamycin for 8 months, in one doxycycline for 1½ years, and in the last two cases a combination of cloxacillin and ampicillin for 6 months. The remaining 13 cases had been treated during short periods with various antibiotics which were changed repeatedly. The antibiotic treatment in these cases is therefore difficult to reconstruct and evaluate.

* Palacos^R cum gentamicin, Essex Läkemedel AB, Sweden. Subsidiary of Schering corporation.

** Septopal^R, Merck, West-germany

All antibiotic treatment was discontinued for at least four weeks prior to the total hip arthroplasty. During this operation five or more tissue biopsies were taken with sterile forceps and each piece placed into a carbon dioxide tube and immediately transported to the bacteriological laboratory for anaerobic and aerobic cultures. After the tissue samples had been taken an antibiotic, usually isoxazolylin-penicillin, was administered and the treatment continued for an average of five months (range 1.5-8 months) (see Table 1). In three of the four cases (No 1, 2, 3) where a positive bacteriological culture was obtained at total hip surgery the antibiotic treatment had to be changed according to the pattern of resistance.

Persisting infection at the time of the total hip replacement

The evaluation of the infection at the time of the total hip replacement was based on the ESR value, the presence of a draining fistula and positive cultures obtained at the time of the total hip arthroplasty. The patients were assigned to one of the following groups:

- I Active infection: positive culture*
- II Probably active infection: negative culture* but elevated ESR which became normal after the total hip replacement and/or a draining sinus.
- III Healed or quiescent infection: negative culture* and preoperative normal ESR.

There were 4 active, 8 probably active and 12 healed or quiescent infections. The last group included five patients with rheumatoid arthritis and an ESR between 30 and 90 mm.

* According to Kamme and Lindberg.¹³

Follow-up

The criteria for healing of the infection were:

- a. A painfree hip
- b. Normalization of the ESR excluding patients with rheumatoid arthritis.
- c. A bone-cement radiolucency less than 2 mm and without progress later than 12 months postoperatively.

At the re-examination antero-posterior views of the hip centralized over the joint and of the pelvis centralized over the symphysis and a lateral view of the hip joint were obtained and compared to the corresponding radiograms taken after the operation 3, 6 and 12 months postoperatively and evaluated with respect to bone-cement lucency, localized bone resorption (scalloping), periosteal reactions and any change of the position of the prosthetic components.
2,5,8

The function was evaluated according to Merle d'Aubigné and Postel (1954)¹⁵ as modified by Charnley (1979)⁸ (Table 2). The patients were grouped into categories A-C according to Charnley (1979). Category A patients were physically fit in all respects regarding function, having no defects other than the affected hip. Category B patients had both hips affected but were otherwise physically fit. Category C was reserved for patients with conditions other than the hip involved that directly impaired the act of walking such as cardiac insufficiency, rheumatoid arthritis, osteoarthritis of the knee etc.

Table 2. Method of grading functional status of the hip

Grade	Pain	Walking ability	Range of motion*
1.	Severe and spontaneous	Bedridden or only able to walk a few meters	0 - 30°
2.	Severe and attempting to walk, prevents all activity	Distance of walking very limited with or without a walking aid	31 - 60°
3.	Tolerable, permits limited activity	Limited but able to stand for long periods	61 - 100°
4.	Present only after activity, disappears quickly with rest	Long-distance walking possible but limited without aid	101 - 160°
5.	Slight or intermittent, decreasing with activity	Walks without aids but limps	161 - 210°
6.	No pain	Walks normally for age	More than 210°

* Passive range: Sum of degrees of flexion, rotation, and abduction-adduction

RESULTS

The patients were followed for an average of 62 months (20-95) after the total hip replacement. All cases had primary wound healing. At follow-up there was no case with clinical, laboratory or radiographic signs of infection. Also, in four of the six patients with rheumatoid arthritis, the ESR value had declined and approached normal values. In the two remaining patients with rheumatoid arthritis the ESR value was about 35 before and after the total hip replacement.

One patient (No 11) developed a small abscess in the lower part of the wound 26 months after the total hip replacement. The abscess was incised and a small amount of pus was drained off and Staphylococcus was cultured. The wound healed after two weeks of cloxacillin treatment which was continued for five months. The patient never experienced any pain, ESR was at the time normal (10 mm/h) and there were no radiographic signs of deep infection. The patient has now been followed for another 19 months, the ESR and the radiograms remain normal and the hip is painfree.

Three patients died from causes other than their hip condition 20, 41 and 85 months postoperatively without any signs of recurrence of the infection.

Table 3. The function of the hip at the re-examination (see also Table 1)

		No. of pat.	Hip score						Average
			1	2	3	4	5	6	
Pain	Cat. A-C	24					9	15	5.6
Walking ability	Cat. A	13				2	5	6	5.3
	Cat. B	3			1	2			3.7
	Cat. C	8	1	1	2	4			3.1
Range of motion	Cat. A-C	24		1	1	7	11	4	4.7

Fifteen patients were completely free from pain. The remaining nine had slight or intermittent pain decreasing with activity.

The walking ability was normal or nearly normal for 11 of the 13 category A patients.

In 11 cases there was no leg discrepancy, in 11 less than 2 cm shortening and in two cases shortening between 2 and 5 cm.

Four out of the 13 category A patients demonstrated a positive Trendelenburg sign whereas it was negative in the rest of this group.

DISCUSSION

The fear of a flare up of a quiescent infection has implied reluctance to total hip surgery in cases with a history of a septic arthritis. Hardinge et al.¹⁰ recommended great restraint and in their report the time elapse from infection to total hip arthroplasty averaged 10 years.



Fig 1A



Fig 1B



Fig 1C

Fig 1 A-C. A man 52 years old (Case 6 in Table 1) had a traumatic dislocation of the hip. Open reduction and fixation of the posterior acetabular fragment was performed. Postoperative florid infection with *Staphylococcus aureus* and *Pseudomonas pyocyanea* resulted in destruction of the hip (1A). After several months of antibiotic treatment, the sinus closed and the ESR dropped from 74 to 31 mm/h, a Brunswik total hip prosthesis was implanted 14 months after the initial trauma (1B). Eight years later the patient was working as a truck driver. Hip score 5-6-4, ESR 9 mm. No radiographic signs of infection or loosening were found (1C).



Fig 2A



Fig 2B



Fig 2C

Fig 2 A-C. A woman 75 years old (case 21 in Table 1) had a femoral neck fracture operated with a Rydell nail (2A). Immediately after the operation the patient developed an abscess with growth of *Staphylococcus aureus*. After one month the patient still had fistulation and pain at rest from the hip. The nail was extracted and the patient was treated with pivampicillin and cloxacillin orally for six months. The radiograms at three months showed collapse and resorption of the femoral neck and osteomyelitic destruction of the upper femur and acetabulum (2B). The ESR was 116 mm/h in the acute phase and decreased to 50 mm/h before a total hip was inserted. At follow-up 64 months after the total hip operation the patient had a hip score of 5-4-5 and clinically and radiographically no signs of infection (2C).

The purpose of this study was to investigate the possibility to reduce this interval or even replace the hip very shortly after a septic arthritis or similar condition, applying the same principles for infected total hip arthroplasties as described by Buchholz et al.^{3,6}

Only cases with definitely verified infection were included in our material. In four cases infection was demonstrated at the time of total hip replacement. In the remaining 20 cases the infection might have been healed at this point. However, in eight of these 20 cases an elevated ESR was normalized after the procedure, indicating that infection might have been present at the time of total hip surgery.

Eighteen of the primary infections were caused by bacteria commonly accepted as pathogenic e.g. *Staphylococcus aureus*, beta hemolytic streptococci, *E.coli*, *Pseudomonas* and *Proteus*. The remaining six cases were caused by bacteria, the pathogenicity of which may be questionable. However, in connection with cemented orthopaedic implants also *Staphylococcus epidermidis*, *Peptococcus magnus* and *Bacillus subtilis* have been demonstrated as the cause of deep infections.^{9,12,13,14,16}

In the investigation presented by Wilson et al.¹⁷ the interval between infection and THR averaged 18 months and the patients had been treated by suction-irrigation drainage and systemic antibiotics for seven weeks. However, the infection persisted (recurred) in 4/36 cases at examination on an average of 12 months after the total hip replacement. In the series by Hardinge et al.¹⁰ the patient was given prophylactic cloxacillin for two weeks. There was no recurrence of the infection on an average of 32 months postoperatively.

The postponement of the reconstruction (averaging 17 months), systemic antibiotic treatment and the use of gentamicin-containing bone cement in our study, may all have contributed to our good

results, and the extremely long delay recommended by Hardinge et al. seems unwarranted.

The function following total hip surgery in our series of patients was satisfying (Table 2) and superior to that reported after resection arthroplasty.⁷

SUMMARY

Twenty-four patients with active, or quiescent septic coxitis have been treated with THR using gentamicin-containing bone cement and longstanding antibiotic treatment. At the follow-up averaging 62 months postoperatively there were no recurrences of the infection and the functional results were good.

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V

Total hip joint arthroplasty with gentamicin-impregnated cement

A clinical study of gentamicin excretion kinetics

by

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ABSTRACT

The excretion pharmacokinetics of gentamicin (GM) following total hip joint arthroplasty with GM-impregnated bone cement were studied in ten patients. The patients received 0.5-1.1 g of GM. Twenty-four-hour portions of urine were collected for up to 60 days after operation. GM concentrations in urine were initially 8-25 mg/l, and during the first four days the excretion ranged from 0.7 to 25 mg/day. On the 30th day drug levels in the urine were 0.5-1.0 mg/l, and the excretion was 0.5-1.0 mg/day. The GM excretion-time curve consisted of an initial rapid phase that terminated four to six days after operation, with a half-life of 0.65 days, and a slow phase with a half-life of 7.5-73.0 days (mean, 16 days). From the area under the excretion-time curve and from extrapolation of the registered terminal phase, it was calculated that 5%-18% (mean, 13%) of the GM administered was accounted for. Thus, a major portion of the drug was unaccounted for. Data obtained two years after operation suggested that the half-life of the terminal phase is much longer (>240 days) than that calculated from data obtained during the first two months after operation. It was calculated that the surface area of the cement would be in excess of 150 cm^2 and that the volume of an interface tissue layer 1 mm thick would be approximately 15 cm^3 . Thus, at three weeks, when the daily excretion was approximately 1 mg/24 hours, $67 \text{ } \mu\text{g}/\text{cm}^3/\text{day}$ of GM would be available for antimicrobial action at a tissue-cement interface 1 mm thick.

INTRODUCTION

Deep infection is a serious complication after total hip joint arthroplasty (THA). In the 1960s and the beginning of 1970s the post-operative infection rate in large series was 8%-15%.^{5,7} Strict hygienic routines, clean-air operating enclosures, and the use of intraoperative systemic antibiotic prophylaxis have reduced the

infection rate to 1% or less.^{7,8,12,19} In 1970 Buchholz and Engelbrecht⁴ introduced the concept of addition of antibiotics to bone cement. In a clinical randomized study¹⁴ gentamicin (GM)-impregnated bone cement was shown to be at least as effective as systemic antibiotic therapy (0.4% versus 1.6%, respectively). The long-term effect of antibiotic-impregnated cement on hematogenous infection has not been proved.^{3,10,21}

The release of GM from bone cement in vitro has been thoroughly investigated, while in vivo pharmacokinetic calculations are scarce. In the present study the in vivo pharmacokinetics of GM excretion in urine following THA with GM-impregnated cement were investigated, and the influence of GM accumulation in renal parenchyma on the excretion kinetics was evaluated.

MATERIAL AND METHODS

Ten patients (Table 1) underwent THA (Lubinus prosthesis) for osteoarthritis with polymethylmethacrylate (PMMA) cement containing GM sulphate corresponding to 0.5 g of GM base/40 g of PMMA powder (Palacos, Schering Corporation, New Jersey, USA). The operations were performed at the Department of Orthopaedic Surgery, University Hospital, Lund, Sweden. The patients had not previously received aminoglycosides and had been without other antibiotics and diuretics for at least one month prior to operation.

A urinary catheter was placed immediately prior to operation. Urine was collected in four-, twelve-, or 24-hour portions at the times specified in Figures 1-3, beginning immediately after the first prosthetic component was cemented. The amount of cement used was determined, and the total GM dose was calculated for each patient (see below). No other antimicrobial agents were given for two months after operation. There was no restriction in food and drink except for the

TABLE 1. Characteristics of 10 patients following total hip replacement with gentamicin (GM) in the PMMA bone cement

Patient	Sex	Age (Yrs)	Weight (kg)	S-creatinine ($\mu\text{mol/l}$)		Bone cement* (Palacos, g)	Gentamicin*	
				Pre-op.	2 yrs later		mg	mg/kg
1	M	66	97	124	117	81.5	725	7.5
2	F	44	62	65	69	73.0	650	10.5
3	F	45	87	70	ND	55.0	490	5.6
4	F	56	70	75	55	68.0	605	8.6
5	F	69	57	71	62	69.5	619	10.9
6	F	72	92	73	74	64.5	574	6.2
7	F	66	57	70	70	60.2	536	9.4
8	F	70	60	72	65	69.0	614	10.2
9	M	54	60	74	84	71.0	632	10.5
10	M	57	65	60	ND	122.0	1086	16.7
Mean		60	-	-	-	73.4	653	9.6

* The PMMA bone cement contained 0.89 per cent active gentamicin (see materials and methods section).

first 24 hours. The patients were immobilized in bed for 24 hours and then mobilized according to general principles.

Two years after operation the patients were examined; examination included a functional test,⁶ measurement of serum creatinine levels and the erythrocyte sedimentation rate, and roentgenograms of the hip. Twenty-four-hour portions of urine for determination of GM excretion were also collected.

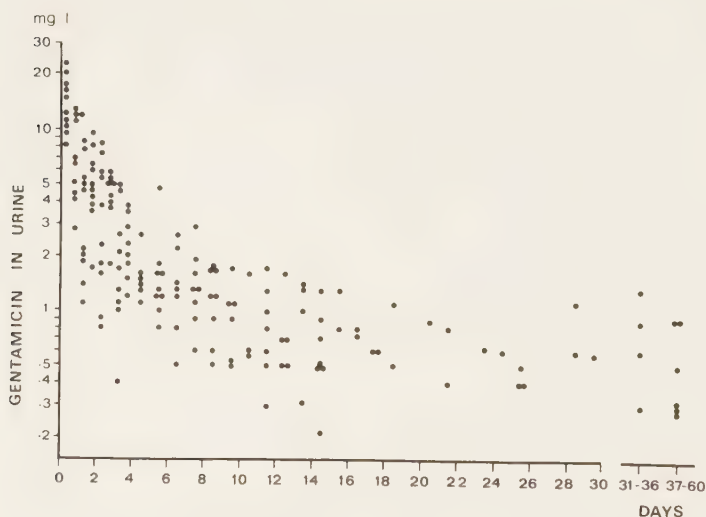


Fig 1. GM concentrations in urine following total hip joint arthroplasty with 0.9% GM base in the PMMA cement (n = 10 patients; mean GM dose, 9.6 mg/kg (range, 5.6-16.7 mg/kg; individual values).

Determination of gentamicin concentrations

The urine portions were measured to the nearest milliliter, and samples were stored at -20° . All samples were analyzed simultaneously against the same standard solutions. An agar diffusion technique^{15,16} with standard solutions prepared in 0.07 M phosphate buffer containing 0.15 M NaCl was employed. The same buffer was used to prepare two-fold dilutions of the urine samples. The latter were diluted until parallelism with the standard curve in a semilogarithmic graph was achieved. To identify aminoglycoside activity in samples with low antibacterial activity (<0.1 mg/l), these samples were treated with

cellulose phosphate powder (ICN, Biochemicals, Cleveland, Ohio) and checked for loss of activity.²²

The sensitivity of the assay (using a *Micrococcus* as test strain and 7-mm wells) was 0.06 mg/l and the imprecision (coefficient of variation) 6%.

Calculations and pharmacokinetics

A bag of Palacos powder with GM (40.5 g) was mixed with 20 ml of Palacos liquid (monomer) (18.8 g), producing a theoretic total weight of 59.3 g. The cement was placed in a plastic bag and allowed to harden at +37° for ten minutes, after which it was weighed. Since some of the monomer evaporate, the final weight was lower than the theoretic weight. The procedure was repeated, and the mean of the two observations was used to calculate the GM potency of the finished cement. The weights were 56.6 and 55.9 g, respectively (mean 56.25 g). Thus, the cement contained approximately 0.89% active GM.

To standard Lubinus prosthesis 73 g of Palacos cement (corresponding to the average amount used in the 10 patients) was applied in vitro and allowed to harden. At the Institute of Technology, University of Lund, the prosthesis was cut at eight places, and the cross sections obtained were used to calculate the surface area of the cement. The area was approximately 150 cm².

The excretion of GM, expressed as mg/hour or mg/day, was calculated by multiplying concentration by urine volume and dividing by time. Pharmacokinetic calculations were performed according to the method of Gibaldi and Perrier¹¹ and are further specified in Table 2.

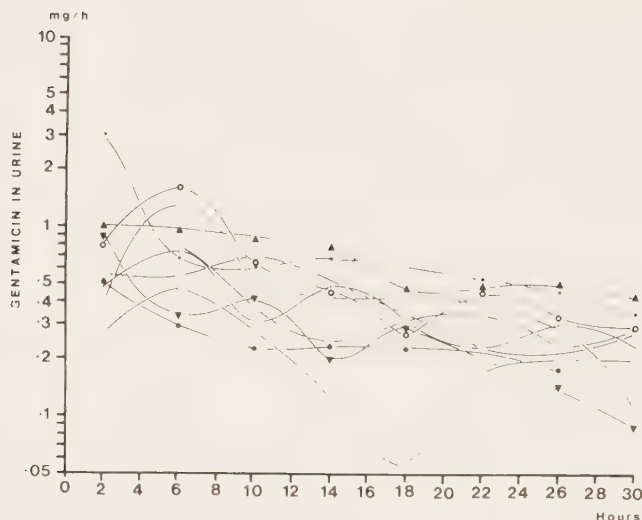


Fig. 2. Excretion of GM in urine (mg/hour) following total hip joint arthroplasty with 0.9% GM base in the PMMA cement (n = 10 patients; mean GM dose, 9.6 mg/kg (range, 5.6-16.7 mg/kg; 4-hour portions of urine, individual excretion curves).

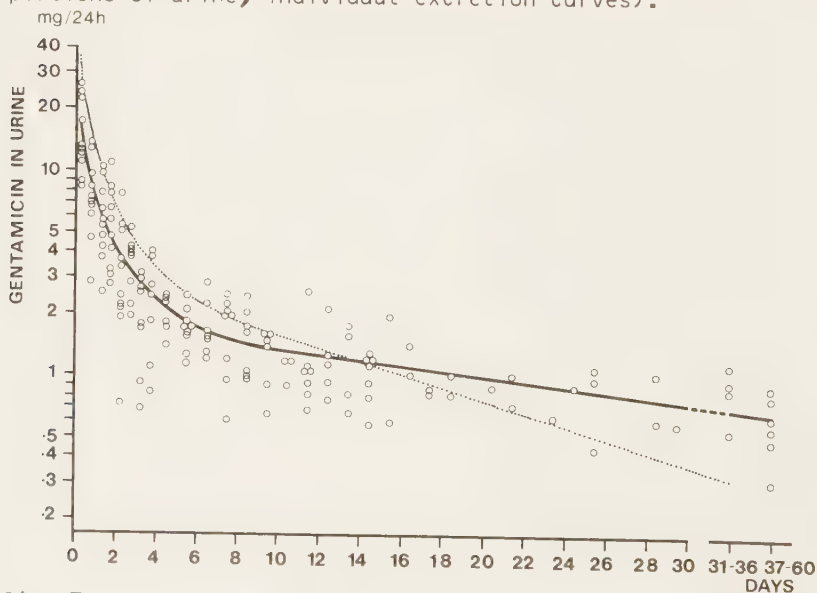


Fig. 3. Excretion of GM in urine (mg/day). Individual values and mean curve (unbroken line) in 10 patients following total hip joint arthroplasty with 0.9% GM base in the PMMA cement (mean dose, 9.6 mg/kg; range, 5.6-16.7 mg/kg). Dotted line = mean excretion curve in 16 patients following 5-22 days of parenteral GM therapy for various infections (total dose, 15-60 mg/kg) (see Kahlmeter et al.¹⁸).

TABLE 2. Characteristics of the excretion of gentamicin (GM) in urine following total hip joint replacement with gentamicin in the PMMA bone cement

Patient	Initial excretion phase (C - 4 days)			Slow excretion phase (5 days - ∞)			The amount of GM accounted for in urine in per cent of given
	α^1 (days ⁻¹)	$T_{1/2}$ (days)	GM recovered (mg) ²	β^1 (days ⁻¹)	$T_{1/2}$ (days)	GM recovered (mg) ³	
1	1.015	0.7	31.4	0.082	8.5	30.6	9
2	1.169	0.6	21.1	0.010	73.0	97.9	18
3	0.443	1.6	19.1	0.042	16.6	41.9	12
4	0.806	0.9	19.4	0.054	12.9	40.6	10
5	1.055	0.7	35.7	0.025	27.6	75.3	18
6	1.471	0.5	19.3	0.023	30.8	58.7	14
7	1.468	0.5	10.8	0.039	17.8	47.2	11
8	0.461	1.5	24.8	0.022	31.1	86.2	18
9	1.373	0.5	45.3	0.091	7.6	18.7	10
10 ⁶	1.340	0.5	16.1	0.042	16.6	40.9	5
Mean ⁵	1.060	0.65	24.3	0.043	16.1	53.8	13

1. α and β are the disposition rate constants of the initial and slow excretion phases, respectively ($C = Ae^{-\alpha t} + Be^{-\beta t}$)
2. GM recovered in urine during the first 96 hours after insertion of the joint prosthesis (all urine collected as consecutive 4-hour portions)
3. GM recovered in urine from the 96th hour and onwards: calculated as the extrapolated area under the excretion time curve from the 96th hour to infinity from C_{96}/β
4. Calculated as the actual amount of GM recovered 0 - 4 days postoperatively plus the extrapolated amount of GM under the excretion time curve from 5 days and onwards in per cent of the total amount of GM in the PMMA cement
5. Mean half lives calculated as in 2/ mean α and mean β , respectively
6. The hip joint dislocated immediately after the operation, closed reduction was performed and traction applied for 6 weeks

RESULTS

The characteristics of the ten patients are shown in Table 1. There was no evidence of renal function deterioration for two years after operation as measured by serum creatinine levels. The patients received 55-122 g of Palacos (mean 73.4 g) and, thus, 490-1086 mg of GM (mean, 653 mg), corresponding to 5.6-16.7 mg/kg body weight (mean, 9.6 mg/kg).

The GM concentrations in urine are shown in Figure 1. During the first four days the GM levels declined rapidly but were above 1 mg/l (20.4-0.4 mg/l) in the majority of the urine portions collected. From the fifth day the concentrations declined less rapidly, and 31-60 days after operation the levels were still 1.7-0.3 mg/l.

Figure 2 shows the individual GM excretion-time curves (mg/hour) zero to 30 hours after operation. In all instances they were irregular and alternately dominated by absorption and disposition. When expressed as daily excretion (Fig. 3) two major disposition phases were apparent. The more rapid phase, roughly terminated at four days, exhibited a disposition half-life of 16 hours (12-38 hours), and the mean amount of GM recovered during this period was 24.3 mg (range, 10.8-45.3 mg) (Table 2). The amount of GM excreted during the first 24 hours corresponded to an average of 2% (range, 0.9%-3.9%), while that recovered during the first four days corresponded to 4% (range, 1.5%-7.2%) of the GM administered. The half-life of the second phase varied from seven to 73 days (mean, 16 days). From the fifth to the tenth day the daily excretion of GM was 3.0-0.6 mg/24 hours. From the 30th to the 60th day the excretion was 0.9-0.3mg/24 hours. The amounts of GM recovered in urine after operation, measured in total for the first four days and extrapolated from the individual excretion-time curves from the fifth day (Table 2), corresponded to 13% (range, 5%-18%) of the GM given in the bone cement.

In eight of the ten patients a 24-hour portion of urine was collected two years after operation. In seven patients the GM concentration was below the detectable level (<0.06 mg/l). In one patient (Case 5) the GM concentration was 0.08 mg/l, and the excretion for 24 hours was 0.12 mg. A rough extrapolation of the excretion-time curve yielded a half-life of the slow phase of 240 days and a total amount of GM excreted during the two years of 275 mg, corresponding to 44% of the GM given in the PMMA bone cement.

DISCUSSION

Several systemic and local antibiotic regimens have been employed in the prevention of infection after THA.^{6,14} The GM-containing bone cement⁴ introduced in 1970 has been shown to be effective in the prevention of early infection after THA and in revisions of infected prostheses.¹⁴ However, its effectiveness in the prevention of hematogenous infection is as yet unproved. In animal models in which *Staphylococcus aureus* and/or various gram-negative bacteria were either introduced directly in the bone cavity with the cement or injected intravenously 30 minutes to six weeks after operation, the infection was successfully prevented when "early infection" was simulated.^{3,10,21} When *Staphylococcus aureus* were injected intravenously six weeks after operation Elson and co-workers¹⁰ found no difference between the experimental and control groups, but the incidence of deep infection in the control group was low.¹⁰ Blomgren and Lindgren² recorded a high incidence of deep infection in both groups. Thus, it seems that in animal models the long-term protective effect of GM bone cement is doubtful.

The goal of the present study was to investigate the in vivo pharmacokinetics of GM released from bone cement and to use the excretion data to calculate the amount of GM available for antibacterial action at the interface between cement and tissue. The second goal

was to determine the influence of GM accumulation in and slow release from renal parenchyma on the terminal excretion phase in urine.

Since the excretion profile of GM in urine following the introduction of GM bone cement into the body is heavily influenced by the general pharmacokinetics of gentamicin, these characteristics are outlined. GM is excreted by glomerular filtration alone. Approximately 10%-15% of a single intravenous dose is reabsorbed by the proximal tubule cells and then bound intracellularly. The process is thought to be capacity-limited. The drug is firmly bound and only slowly released. The disposition curves in serum and urine following parenteral administration are biphasic. In patients with normal renal function the rapid phase exhibits a glomerular filtration rate (GFR)-dependent half-life of 1.5-2.0 hours. The terminal phase, apparent both in serum and urine, is GFR-independent and probably governed by intracellular binding kinetics, renal blood flow, etc. It exhibits a half-life of 30-60 hours in healthy volunteers and of 150-200 hours in hospitalized patients (for reviews of aminoglycoside pharmacokinetics, see Kahlmeter^{15,17}).

In vitro, the release of GM from PMMA cement is biphasic; the initial phase, with a half-life of 24-48 hours, is terminated between the tenth and 20th day; the second phase exhibits a half-life of approximately 30 days.¹³ The rate of release increases with increasing cement surface¹³ and is unaffected by pH,¹ and elution into buffered saline and serum is equal.²⁴ In long-term in vitro studies the release of GM has been demonstrated to continue for at least five years.^{24,25} However, only 5%-10% of the GM in the cement is released readily, while the remainder is leached slowly.¹ If the cement is cut to open a new surface, the rate of release increases.¹ Bayston and Milner¹ presented evidence suggesting that the cement acts like a type II b matrix, i.e., the drug diffuses through the entire matrix rather than through formed capillaries.

In vivo GM released from the cement would either be absorbed and reach the circulation or be "lost" in wound secretion. As shown in Figure 2, the excretion-time curves exhibit an absorption phase for half of the patients, following which the excretion curves are irregular; disposition and absorption phases alternate. Although the general trend is toward disposition, it was evident from the individual curves that the absorption of drug varied widely during the entire observation period, from one four-hour portion of urine to the next and also from one day to the next. It is reasonable to assume that in the early stages the amount of drug that reaches the circulation is influenced by variations in the degree of secretion and bleeding and in the degree of drainage of secretions and haematoma. Later, such factors as mechanical strain, exertion, and, thus, blood flow may alter the absorption of GM released from the bone cement.

The in vivo pharmacokinetics of GM following the administration of GM bone cement or beads are further complicated by the fact that two "slow-release systems", the renal tissues and the cement, each of which exhibits biphasic GM excretion, are operating in parallel. As shown in Figure 3, patients who received parenteral GM therapy for an average of ten days exhibited excretion curves similar to those recorded after use of GM bone cement. Since the proximal tubule cells reabsorb and bind some of the GM released from the cement, calculations based on the early part of the urinary excretion curve will underestimate the amount of drug actually released by the cement. Conversely, calculations based on a later part of the curve would overestimate, possibly by as much as twofold, the amount of drug released and thus potentially available to the relevant tissues.

For these reasons the in vivo release of GM from the cement can only be approximated from urinary excretion data unless it can be determined that the calculations were based on data collected during the "true" terminal excretion phase. This was not the case in the

present study. However, it has been confirmed that the release of GM from the cement is biphasic and that the cement continues to release GM for long periods. Had the release of GM not continued, the half-lives of the recorded terminal phases would not have exceeded the half-lives recorded in patients receiving parenteral GM.

In the present study the amount of drug released and "lost" in wound secretions was not measured. However, it could not have accounted for more than at most 10% of the GM introduced. Wahlig and co-workers²⁵ recovered an average of 8% of the drug in wound secretions of patients following the insertion of PMMA beads which have a larger surface area and release more GM per time than the bone cement.⁹ Schurman and co-workers²¹ recovered approximately 20% of the GM in urine during five months after the insertion of GM cement in rabbits. In the present study, based on the data collected from zero to 60 days after the insertion of the cement, it was calculated by extrapolation of the recorded terminal phase that 5%-18% of the GM could be accounted for. With the addition of 5%-10% lost in wound secretion, 75%-80% is still not accounted for. Since there is no reason to assume loss by inactivation, biotransformation, or excretion by any other major route, it is assumed that the terminal phase has a considerably longer half-life than that recorded. Data obtained after two years in one of the patients support this hypothesis, suggesting a terminal half-life of at least 240 days in this patient.

Schurman and co-workers²¹ found that GM levels in specimens of knee joint capsule directly overlying the bone cement ranged from 0.15 to 0.6 $\mu\text{g/g}$ of tissue one to six months after implantation of GM cement in rabbits. Hoff and co-workers¹³ compared the GM concentration in various layers of bone between the periosteal and endosteal surfaces at various times after implantation of GM bone cement in canine model. The highest concentrations were recorded 14 days after implantation (40-80 $\mu\text{g/g}$ of tissue) in the layer closest to the

endosteal surface. After 210 days the concentrations were at most 5 $\mu\text{g/g}$ of tissue.¹³ Wahlig and Dingeldein²⁴ measured concentrations of 0.4-33.0 $\mu\text{g/g}$ of connective tissue and spongiosa and decidedly lower concentrations in corticalis 24-69 days after THA with GM bone cement in patients. In all of these studies the tissue specimens were either homogenized and the drug was eluted, or ^{14}C -labeled GM was measured after combustion of the specimens. Neither of these techniques distinguished between free GM and GM trapped in or bound to the tissues, and since aminoglycosides are known to bind to various biologic materials and tissues and are probably inactive when bound, this is an important distinction.^{20,23}

Two to three weeks after insertion of the GM bone cement, the 24-hour excretion of the drug in urine was 1 mg or less. Thus, at most 1 mg of GM/day would be available for antibacterial action at the cement-tissue interface. With a cement area of approximately 150 cm^2 the volumes of interface tissue 0.1, 0.5 or 1.0 mm thick would be 1.5, 7.5, and 15.0 cm^3 , respectively. Thus 670, 134, or 67 μg , respectively, would be available per cubic centimeter of tissue and day. Whether or not this is sufficient to prevent infection from hematogenously disseminated bacteria is not known.

In summary, the present study characterized the in vivo GM excretion profile in urine and determined the levels of excretion and the amount of drug potentially available for antimicrobial action at the cement-tissue interface at various times following the implantation of 0.89% GM bone cement. Moreover, the biphasic release of GM from the cement was confirmed, as well as the irregular absorption of GM released from the cement. The terminal half-life of the excretion profile was considerably longer than would be explained by the uptake of GM in and the slow release from renal parenchyma, proving that the cement continues to release GM in vivo for long periods.

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